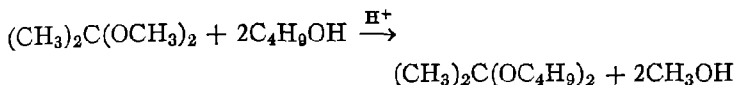


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ACETONE DIBUTYL ACETAL

(Propane, 2,2-dibutoxy-)



Submitted by N. B. LORETTE and W. L. HOWARD.¹

Checked by MAX TISHLER and STANLEY NUSIM.

1. Procedure

A mixture of 312 g. (3 moles) of acetone dimethyl acetal (Note 1), 489 g. (6.6 moles) of butanol, 1.0 l. of benzene, and 0.2 g. of *p*-toluenesulfonic acid is placed in a 3-l. flask. The flask is connected to a packed fractionating column and the solution distilled until the azeotrope of benzene and methanol, boiling at 58°, is completely removed (Note 2). The contents of the boiler are then cooled below the boiling point and a solution of 0.5 g. of sodium methoxide in 20 ml. of methanol (Note 3) is added all at once with stirring. The flask is replaced for further distillation, and most of the remaining benzene is distilled at atmospheric pressure. The pressure is then reduced, and the remaining benzene and unreacted butanol are removed (Note 4). Finally, the pressure is reduced to 20 mm., the last traces of low-boiling materials are taken to the cold trap, and the product is distilled. After a small fore-run, acetone dibutyl acetal is collected at 88–90°/20 mm. The yield is 421–453 g. (74.6–80.3%), n_D^{25} 1.4105, d_4^{25} 0.8315.

2. Notes

1. Commercial acetone dimethyl acetal (2,2-dimethoxypropane) from the Dow Chemical Company was used without further treatment.

2. About 570 ml. of this azeotrope is obtained. The methanol produced may be estimated by washing an aliquot with about

two volumes of water in a graduated cylinder. The methanol content is approximately the difference between the initial volume and that of the residual benzene phase, and about 230 ml. is obtained, depending on the efficiency of fractionation. Other hydrocarbons, e.g., hexane or cyclohexane, can be used for the removal of methanol.

The submitters' distillation was carried out in a 19 x 1200-mm. vacuum-jacketed silvered column fitted with a magnetically operated vapor-takeoff head controlled by a timed relay. The checkers found that a 19 x 340-mm. vacuum-jacketed column fitted with a magnetically operated liquid takeoff and packed with $\frac{1}{4}$ -in. glass Raschig rings was sufficient for carrying out the distillation. The checkers, using a reflux ratio of 2.7 to 1 throughout the distillation, found the total time required to be 19 hours.

Since the required separations are not difficult, any reasonably efficient fractionating column may be used.

3. Other soluble non-volatile bases may be used.

4. It is best to keep the temperature of the distilland below 125–150°, because pyrolysis of the product becomes progressively more serious at higher temperatures. The pressure is reduced to a convenient value when the distilland temperature reaches 125°. For example, a pressure of 200 mm. will allow the condensation of the benzene without resort to special cooling.

3. Methods of Preparation

Acetone dibutyl acetal has been prepared from isopropenyl acetate and butanol,² from butanol and isopropenyl butyl ether obtained from the reaction of butanol with propyne,³ and by orthoformic ester synthesis.^{4,5}

4. Merits of Preparation

The preparation described here is a modification of previously used alkoxyl interchange reactions, but it is more convenient because the use of the azeotrope-forming solvent permits the virtually complete removal of the by-product alcohol under mild conditions. The method is general for most primary and sec-

ondary alcohols, including those with functional groups which are stable under the mild conditions used.

¹ The Dow Chemical Company, Texas Division, Freeport, Tex.

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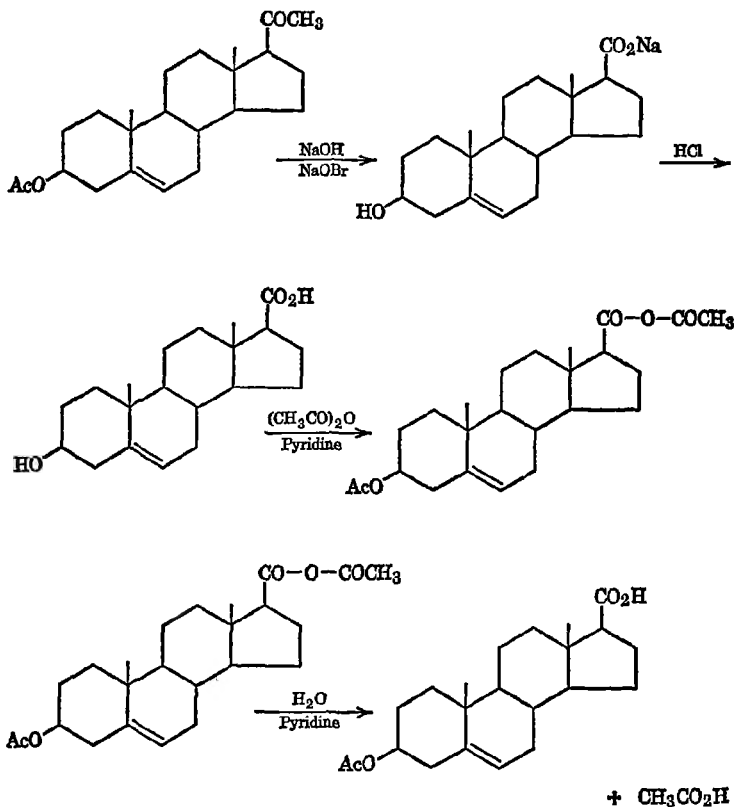
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3 β -ACETOXYETIENIC ACID

(3 β -Acetoxy-5-androstene-17 β -carboxylic acid)



Submitted by J. STAUNTON and E. J. EISENBRAUN.¹

Checked by W. G. DAUBEN and J. H. E. FENYES.

1. Procedure

A solution of 42 g. (1.05 moles) of sodium hydroxide in 360 ml. of water is placed in a 1-l. three-necked, round-bottomed flask

fitted with a mechanical stirrer and a thermometer and is cooled to -5° in an ice-salt bath. The stirrer is started, and 43 g. (0.263 mole) of bromine is added from a separatory funnel at such a rate that the temperature remains below 0° (addition time about 5 minutes). The ice-cold solution is diluted with 240 ml. of dioxane (Note 1) that has previously been cooled to $13-14^{\circ}$ (Note 2). This solution is kept at 0° until required.

A solution of 28.8 g. (0.08 mole) of 3 β -acetoxy-5-pregnen-20-one (pregnenolone acetate) (Note 3) in 1.1 l. of dioxane (Note 1) is diluted with 320 ml. of water and placed in a 5-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer (Note 4). The stirrer is started and the mixture is cooled in ice. When the internal temperature has fallen to 8° , the cold hypobromite solution is added in a steady stream. The temperature of the reaction mixture is maintained below 10° throughout the reaction. A white precipitate begins to form after 10 minutes, and the solution becomes colorless during 1 hour. The mixture is stirred for an additional 2 hours, and then the excess sodium hypobromite is destroyed by the addition of a solution of 10 g. of anhydrous sodium sulfite in 100 ml. of water (Note 5).

The stirrer and thermometer are removed and the flask is fitted with a condenser for reflux. The mixture is heated under reflux for 15 minutes, and the solution, while still hot (90°), is acidified by the cautious addition of 50 ml. of concentrated hydrochloric acid (Note 6). The clear yellow solution is kept at 5° for 24 hours. The crystalline precipitate is collected by suction filtration, washed with water, and dried at 100° at atmospheric pressure. The yield of 3 β -hydroxyetienic acid, m.p. $274-276^{\circ}$, is 18-20 g. An additional 3-5 g. of product can be obtained by subjecting the filtrate to steam distillation until a white precipitate is formed. The etienic acid collected from the cooled solution melts at $268-272^{\circ}$. The total yield is 23-24 g. (91-95%).

The 3 β -hydroxyetienic acid is placed in a 500-ml. round-bottomed flask fitted with a condenser protected with a drying tube and is dissolved with warming in 150 ml. of dry pyridine. After the solution has cooled to room temperature, 20 ml. of acetic anhydride is added; a white crystalline precipitate starts to form

immediately. After the mixture has stood for 18–24 hours, it is treated with 20 ml. of water and boiled until the precipitate has dissolved (Note 7). The clear solution is diluted with 70 ml. of water and allowed to cool. The crystalline product is collected by suction filtration, washed with water, and dried in a vacuum oven at 105°/20 mm. The yield of 3 β -acetoxyetienic acid, m.p. 235–238°, is 23–24 g. Recrystallization from glacial acetic acid gives a purer product, m.p. 238–240°. The yield is 16–18 g. (55–63% based on the amount of pregnenolone acetate used).

2. Notes

1. Dioxane as supplied by Matheson-Coleman Bell Co. was used without purification.

2. The temperature of the hypobromite solution is kept below 10° to avoid the formation of sodium bromate.

3. Pregnenolone acetate (3 β -acetoxy-5-pregnen-20-one) supplied by Syntex S. A., Apartado Postal 2679, Mexico, D. F., was used.

4. It is advisable to carry out any operation involving dioxane in a fume hood.

5. Although this amount of sodium sulfite is sufficient to destroy the excess sodium hypobromite, the solution may still give a positive test with starch-iodide paper because of the presence of peroxides in the dioxane used. It is not necessary to destroy these peroxides before proceeding.

6. The solution should be swirled gently during the addition of the hydrochloric acid. Since this operation causes the dioxane to boil, it must be carried out in a fume hood.

7. The anhydride of etienic acid is hydrolyzed in this process to give the soluble acid. Prolonged boiling should be avoided to prevent extensive attack on the less readily hydrolyzed acetate group.

3. Methods of Preparation

3 β -Hydroxy- Δ^5 -etiocholenic acid has been prepared from pregnenolone acetate by the action of sodium hypoiodite;² by oxidation of the furfurylidene derivative;³ and by oxidation of

the benzyldiene derivative of the 5,6-dibromide followed by debromination.⁴ The side chain of 3 β -hydroxy- Δ^5 -bisornolenic acid has been systematically degraded to give the etienic acid.⁵ Two synthetic approaches have involved, respectively, the replacement of the halogen in 17-chloro-3-acetoxy- Δ^5 -androstene by an alkali metal followed by treatment with carbon dioxide⁶ and the conversion of dehydroandrosterone acetate to its cyanohydrin, which then was successively dehydrated, hydrolyzed, and selectively hydrogenated to furnish 3 β -hydroxyetienic acid.^{7,8}

4. Merits of Preparation

3 β -Acetoxyetienic acid has been found to be particularly suitable for the resolution of alcohols. Thus it was employed by Woodward and Katz for the resolution of 1 α -hydroxydicyclopentadiene;⁹ by Djerassi, Warawa, Wolff, and Eisenbraun for the resolution of *trans*-3-*tert*-butylcyclohexanol;¹⁰ and by Djerassi and Staunton for the resolution of *cis,cis*-1-decalol.¹¹

¹ Department of Chemistry, Stanford University, Stanford, California.

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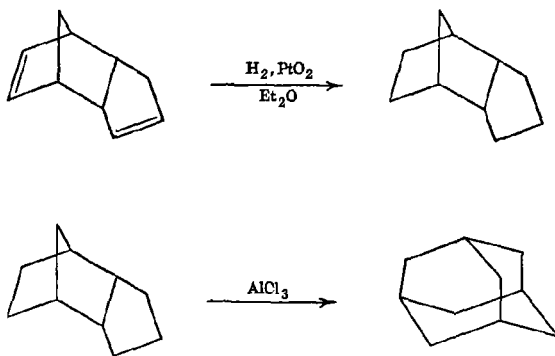
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ADAMANTANE

(Tricyclo[3.3.1.1^{3,7}] decane)

Submitted by PAUL VON R. SCHLEYER, M. M. DONALDSON,
R. D. NICHOLAS, and C. CUPAS.¹

Checked by WILLIAM G. DAUBEN and FRED G. WILLEY.

1. Procedure

A. endo-Tetrahydrodicyclopentadiene. A solution of 200 g. (1.51 moles) of purified dicyclopentadiene (Note 1) in 100 ml. of dry ether containing 1.0 g. of platinum oxide is hydrogenated at 50 p.s.i. hydrogen pressure using a Parr apparatus. The reaction mixture becomes quite warm during the initial stage of the hydrogenation,² and the uptake of 2 mole equivalents of hydrogen requires 4–6 hours. The catalyst is removed by suction filtration, and the filtrate is distilled at atmospheric pressure through a 30-cm. Vigreux column.

When the removal of the ether is complete, the condenser at the top of the column is replaced by a wide-diameter adapter the bottom of which is placed in a receiver flask immersed in an ice bath. The adapter is heated (Note 2) to prevent premature solidification of the distillate. The distillation is continued and the *endo*-tetrahydrodicyclopentadiene, b.p. 191–193°, is collected.

The yield is 196–200 g. (96.5–98.4%). The melting point depends on the purity of the starting material but generally is above 65°.

B. Adamantane. In a 500-ml. Erlenmeyer flask having a 24/40 standard taper joint are placed 200 g. (1.47 moles) of molten *endo*-tetrahydrodicyclopentadiene and a magnetic stirring bar. A well-greased inner joint (2.2 x 15 cm., 24/40) is fitted into the top of the flask to serve as an air condenser, and 40 g. of anhydrous aluminum chloride is added through the opening (Note 3). The reaction mixture is simultaneously stirred and heated at 150–180° (Notes 4, 5) by means of a combination magnetic stirrer-hot plate. Aluminum chloride sublimes to the top of the flask, especially at the beginning of the reaction, and the accumulated sublimate is, from time to time, pushed down into the reaction liquid. After the mixture has been heated for 8–12 hours, the flask is removed from the hot plate-stirrer and the black contents upon cooling separate into two layers. The upper layer, a brown mush of adamantane and other products, is decanted carefully from the lower black tarry layer into a 600-ml. beaker. The Erlenmeyer flask is rinsed five times with a total of 250 ml. of petroleum ether (b.p. 30–60°) with decantation into the same beaker (Notes 6, 7). The petroleum ether suspension is warmed until all the adamantane is in solution; there should be an appreciable excess of solvent. The solution is decolorized by careful addition of 10 g. of chromatography-grade alumina, the hot solution filtered, and the alumina and the beaker washed thoroughly with solvent. The nearly colorless filtrate (Note 8) is concentrated to a volume of about 200 ml. by distillation and then cooled in a Dry Ice-acetone bath. The solid adamantane is removed by suction filtration and there results 27–30 g. (13.5–15.0%) of crystals, melting point about 255–260° (Notes 9, 10). One recrystallization from petroleum ether raises the melting point to 268–270° (Notes 11, 12).

2. Notes

1. Technical grade dicyclopentadiene is purified by distillation at water pump pressure through a 30-cm. Vigreux column, and

the fraction boiling at 64–65°/14 mm. (72–73°/22 mm.) is used in the reaction. The best material is solid or semisolid at room temperature.

2. The adapter can readily be heated by placing an infrared lamp above it.

3. The evolution of heat initially observed is due to the exothermic rearrangement of *endo*-tetrahydrodicyclopentadiene to its *exo*-isomer.³

4. The temperature of the reaction is followed by inserting a thermometer into the reaction flask through the joint.

5. Other methods of heating and stirring may be used but are more troublesome because of the tendency of aluminum chloride to sublime and clog top-mounted stirrers.

6. If appreciable amounts of tar have been transferred to the beaker, repeat the decantation and washing process into a clean beaker.

7. The tarry flasks and beakers can be cleaned easily with acetone. *Do not use water* until all the tar has been removed.

8. If necessary, the filtrate should be warmed to dissolve all the adamantane.

9. The melting point must be taken in a sealed capillary, and the sealed portion must be completely immersed in the liquid of the melting-point bath.

10. Additional adamantane, 2–6 g., can be obtained by distilling the mother liquors through a 10-cm. Vigreux column and chilling the fraction boiling between 180° and 200°. The filtrate from the collection of the second portion of adamantane consists mostly of *exo*-tetrahydrodicyclopentadiene.³ The amount of this fraction, 30–100 g., depends on the severity of the rearrangement conditions. Much non-distillable residue is obtained. Conversion of the 180–200° fractions to adamantane is brought about by treating them with aluminum chloride as before, and the yields are comparable.

11. The recrystallization is not necessary unless material of the highest purity is desired.

12. 1-Methyladamantane and 1,3-dimethyladamantane can be prepared by analogous isomerizations.⁴

3. Methods of Preparation

Adamantane can be isolated from petroleum, where it is found in minute yield.⁵ Two multistep syntheses starting with tetraethyl bicyclo[3.3.1]nonane-2,6-dione-1,3,5,7-tetracarboxylate have been reported.⁶ Also, starting with *endo*-tetrahydrodicyclopentadiene, it has been found that a catalyst composed of aluminum chloride and hydrogen chloride will bring about the rearrangement to adamantane in 30–40% yield, but the reaction must be performed in a hydrogen atmosphere at high pressure.⁷ A recent patent describes the conversion in up to 30% yield using a boron trifluoride-hydrogen fluoride catalyst under pressure.⁸ The present method is based on the published procedure of the submitters and is the preferred method by virtue of the greater convenience.⁴

¹ Department of Chemistry, Princeton University, Princeton, New Jersey.

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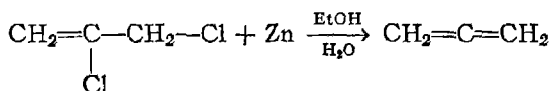
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ALLENE



Submitted by H. N. CRIFFS¹ and E. F. KIEFER.²

Checked by W. E. RUSSEY, R. D. BIRKENMEYER, and F. KAGAN.³

1. Procedure

A 1-l. three-necked flask is equipped with a Hershberg stirrer operating in a ground-glass bearing (Note 1), a 250-ml. pressure-equalizing dropping funnel, and a coil condenser. The exit from the condenser is connected to a train consisting of a trap (of at least 50-ml. capacity below the bottom of the inlet tube) cooled in ice, a drying tube (about 6 in. long by 1 in. I.D.) filled with indicating Drierite and calcium chloride, an efficient trap of at least 150-ml. capacity cooled in Dry Ice-acetone to -70° or below, and a drying tube containing Drierite. A mixture of 95% ethanol (400 ml.), water (80 ml.), and 300 g. (4.6 g. atoms) of zinc dust is placed in the reaction flask. The addition funnel is charged with 260 g. (2.34 moles) of 2,3-dichloropropene (Note 2), the reaction mixture is stirred and heated to reflux, and the 2,3-dichloropropene is added dropwise at such a rate that reflux is maintained without external heating (2-3 hours). After the addition is complete, heating is resumed for 1 hour. The ice-cooled trap is warmed to about 25° , and the residual allene is purged from the reaction flask with a very slow stream of nitrogen.

The trap cooled in Dry Ice-acetone contains about 105 g. of crude product which, when distilled through a column packed with glass helices (Note 3), yields about 75 g. (80%) of allene (Note 4). No external heat is needed during the distillation. The distillation flask is allowed to warm to room temperature,

the distillation beginning at a liquid temperature of -34° and virtually stopping at about 10° . The distilled product contains no detectable ethanol, water, 2,3-dichloropropene, or methylacetylene as determined by gas-liquid chromatography (Note 5).

2. Notes

1. The stirrer should be smooth running and gas-tight. The stirring motor (air-driven) should have a high torque because the reaction mixture tends to agglomerate as the reaction proceeds.

2. 2,3-Dichloropropene from Distillation Products or Columbia Chemicals was employed.

3. A vacuum-jacketed column 1 ft. long by 1 in. I.D. packed with glass helices (4 mm. O.D.) is satisfactory for this distillation. It is fitted with a cold finger in the top of the column cooled by means of acetone that has been cooled in a Dry Ice bath. The fraction cutter is jacketed and similarly cooled. A small circulating pump is used to circulate acetone successively through copper coils in a Dry Ice bath, the fraction cutter, and the cold finger. When the fraction cutter is full, the bottom may be attached to a cooled, evacuated gas cylinder and the allene sucked into the cylinder.

4. The allene contains up to 3% of 2-chloropropene, determined by its vapor-phase infrared spectrum and by vapor-phase chromatography (cf. Note 5).

5. The checkers used an F and M Model 500 gas chromatographic apparatus (F and M Scientific Corporation, P. O. Box 245, Avondale, Penn.) equipped with a polyester column (pentaerythritol adipate, 20% W/W on Chromasorb P, LAC-2-R446) 1 ft. by $\frac{1}{4}$ in. O.D., helium flow 45 cc. per minute, column temperature 50° , block temperature 215° , injector temperature 225° . This system was able to separate allene from methylacetylene and 2-chloropropene.

3. Methods and Merits of Preparation

Although many routes to allene are described in the literature, most preparations give a mixture of allene and methylacetylene.

The virtue of the present preparation, which is essentially that described by Gustavson and Demjanoff,⁴ is that it gives allene in a reproducible manner with 2-chloropropene as its only impurity.

Allene is an extremely useful reagent for cycloaddition reactions giving cyclobutane derivatives.⁵ Allene dimer is also a useful and versatile starting material.⁶

¹ Contribution No. 566 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

² Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California. Present Address: Department of Chemistry, University of Hawaii, Honolulu, Hawaii.

³ The Upjohn Company, Kalamazoo, Michigan.

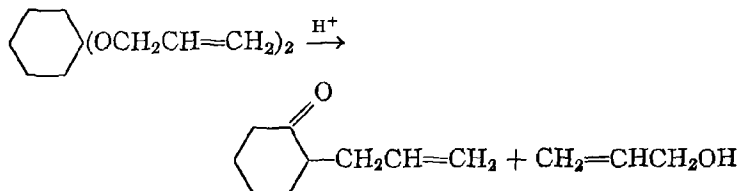
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2-ALLYLCYCLOHEXANONE

(Cyclohexanone, 2-allyl-)



Submitted by W. L. HOWARD and N. B. LORETTE.¹

Checked by MELVIN S. NEWMAN and W. S. GAUGH.

1. Procedure

A solution of 196 g. (1 mole) of cyclohexanone diallyl acetal (Note 1), 150 g. of toluene, and 0.10 g. of *p*-toluenesulfonic acid is distilled through a good fractionating column (Note 2). In about 3 hours, 110 g. of distillate boiling at 91–92° (Note 3) is obtained and the temperature in the head then rises abruptly.

The residue in the distilling flask is cooled and washed with 5 ml. of aqueous potassium carbonate to remove the acid. The remaining solution is passed through a filter containing anhydrous powdered magnesium sulfate and returned to the still. Most of the remaining toluene is removed by distillation at 100 mm. pressure (b.p. 52°). The receiver is changed, the pressure is reduced to 15 mm., and the last of the toluene is collected in a cold trap. The residual oil is rapidly vacuum-distilled to separate the product from a higher-boiling residue. Redistillation yields 117–126 g. (85–91%) of 2-allylcyclohexanone, b.p. 86–88°/15 mm., n_D^{25} 1.4670.

2. Notes

1. The preparation of cyclohexanone diallyl acetal is described on p. 34.
2. A 14-in. helices-packed column is sufficient.
3. This distillate is the azeotrope of toluene and allyl alcohol whose composition is about 50% allyl alcohol by weight.²

3. Methods of Preparation

2-Allylcyclohexanone has been prepared from the sodium derivative of cyclohexanone by alkylation with allyl bromide³ or with allyl iodide,⁴ and by ketonic hydrolysis of ethyl 1-allyl-2-ketocyclohexanecarboxylate.^{5,6}

4. Merits of Preparation

This procedure, when combined with the preparation of allyl ketals (p. 34), provides a general method for obtaining allyl substitution alpha to a carbonyl group. A discussion of some of these applications, as well as the vinyl allyl ether rearrangement which is involved, has been given by Hurd and Pollack.⁷ Also, the procedure can be repeated to allow the introduction of more than one allyl group.

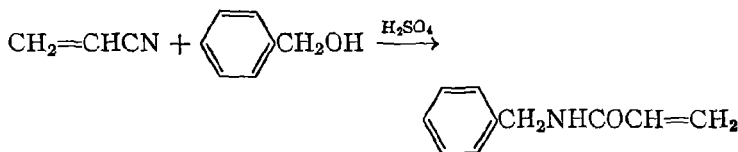
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N-BENZYLACRYLAMIDE

(Acrylamide, N-benzyl-)



Submitted by CHESTER L. PARRIS.¹

Checked by WILLIAM E. PARIHAM, WAYLAND E. NOLAND, and
 JOAN M. WEINMANN.

1. Procedure

In a 1-l., three-necked, round-bottomed flask equipped with a sealed Hershberg stirrer,² a 125-ml. dropping funnel, and a thermometer is placed 200 g. (250 ml., 3.78 moles) of acrylonitrile (Note 1). The flask is immersed in an ice-water bath, and then 75 ml. of concentrated sulfuric acid is added dropwise over a period of about 1 hour while the temperature is maintained at 0–5°. From a clean dropping funnel (Note 2), 108.1 g. (105 ml., 1.0 mole) of benzyl alcohol (Note 3) is added dropwise over about 1 hour at the same temperature. The clear, yellow mixture is held below 5° for about 3 hours longer and is then allowed to warm slowly to room temperature. After 2 days of stirring at room temperature the mixture is poured into a 2-l. separatory funnel containing about 1 l. of water and chopped ice. The mixture is shaken thoroughly and the resulting oil is taken up with 200 ml. of ethyl acetate. The aqueous phase is separated and

extracted twice more with 200-ml. portions of solvent. The organic extracts are combined and washed successively with four 250-ml. portions of saturated sodium chloride solution, four 250-ml. portions of saturated sodium bicarbonate solution, and again with four portions of the salt solution. The neutral ethyl acetate extract is dried over 20 g. of anhydrous magnesium sulfate and filtered. The filtrate is concentrated and the residue is distilled under reduced pressure. A fore-run of 1-3 g. of semisolid is obtained up to $120^{\circ}/0.02$ mm. The product is then collected as a light-yellow oil, b.p. $120-130^{\circ}/0.01-0.02$ mm., which solidifies in the chilled receiver. The distillate (97-101 g.) is melted on a steam bath and dissolved in a mixture of 50 ml. of benzene and 50 ml. of hexane. The solution is transferred quantitatively to a 500-ml. Erlenmeyer flask and the solvent evaporated on a steam bath. The oily residue is placed in a refrigerator for at least 1 day to ensure complete crystallization. The white solid is transferred to a Büchner funnel with the aid of a little ice-cold hexane. After drying in air, the yield is 95-100 g. (59-62%) of N-benzylacrylamide, m.p. $65-68^{\circ}$ (Note 4).

2. Notes

1. Commercial acrylonitrile from American Cyanamid Company was redistilled, b.p. $77-78^{\circ}$.

2. The dropping funnel which has been wetted with sulfuric acid should be washed and thoroughly dried, or a fresh funnel employed.

3. Benzyl alcohol from Fisher Scientific Company was used without further purification.

4. The product is of suitable purity for further reactions. It may be obtained analytically pure, m.p. $70-72^{\circ}$, by recrystallization from benzene. The reported melting point is 69° .³

3. Methods of Preparation

N-Benzylacrylamide has been prepared by dehydrohalogenation of N-benzyl- β -chloropropionamide with aqueous potassium hydroxide,³ and by the reaction of acetylene with carbon mon-

oxide and benzylamine.⁴ The procedure described is the method of Parris and Christenson.⁵

4. Merits of Preparation

The alternative methods of preparation of N-benzylacrylamide are reported in patents, and no yields are given. One of them requires two steps and costlier intermediates; the other appears to be more suitable for plant than for laboratory preparation. The procedure presented involves a simple, one-step reaction taking place under mild conditions, employing inexpensive reactants and affording satisfactory yields.

The N-alkylation of nitriles with aralkyl alcohols, a special case of the Ritter reaction,⁶ is a novel general reaction. The following compounds were prepared by this procedure in the corresponding yields: N-benzylacetamide (48%), N-(2,4-dimethylbenzyl)-acetamide (40%), N-(4-methoxybenzyl)-acetamide (60%), N,N'-diacrylyl-*p*-xylene- α - α' -diamine (64%), N,N'-diacetyl-4,6-dimethyl-*m*-xylene- α , α' -diamine (62%).

The title compound is of special interest and utility as a polymerizable monomer.

¹ Pittsburgh Plate Glass Company, Springdale, Pa.

² E. B. Hersberg, *Ind. Eng. Chem. Anal. Ed.*, **8**, 313 (1936).

³ G. Kranzlein and M. Corell (to I. G. Farbenindustrie, Akt.-Ges.), Ger. pat. 752,481 (Nov. 10, 1952).

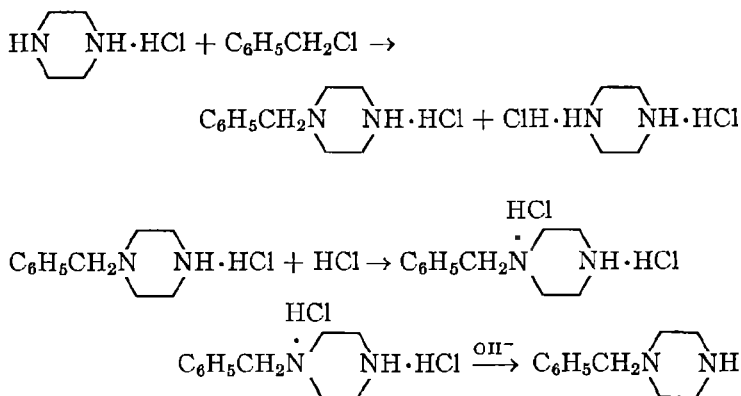
⁴ E. H. Specht, A. Neuman, H. T. Neher (to Rohm and Haas Co.), U. S. pat. 2,773,063 (Dec. 4, 1956).

⁵ C. L. Parris and R. M. Christenson, *J. Org. Chem.*, **25**, 331, 1888 (1960).

⁶ R. M. Luskin and J. J. Ritter, *J. Am. Chem. Soc.*, **72**, 5577 (1950).

1-BENZYLPIPERAZINE

(Piperazine, 1-benzyl-)

Submitted by J. CYMERMAN CRAIG and R. J. YOUNG.¹

Checked by JAMES CASON and TAYSIR JAOUNI.

1. Procedure

A solution of 24.3 g. (0.125 mole) of piperazine hexahydrate in 50 ml. of absolute ethanol, contained in a 250-ml. Erlenmeyer flask, is warmed in a bath at 65° as there is dissolved in the solution, by swirling, 22.1 g. (0.125 mole) of piperazine dihydrochloride monohydrate (Note 1). As warming in the bath at 65° is continued, there is added during 5 minutes, with vigorous swirling or stirring, 15.8 g. (14.3 ml., 0.125 mole) of recently distilled benzyl chloride. The separation of white needles commences almost immediately. After the solution has been stirred for an additional 25 minutes at 65°, it is cooled, and the unstirred solution is kept in an ice bath for about 30 minutes. The crystals of piperazine dihydrochloride monohydrate are collected by suction filtration, washed with three 10-ml. portions of ice-cold

absolute ethanol, and then dried. Recovery of the dihydrochloride is 21.5–22.0 g. (97–99%) (Note 2).

The combined filtrate and washings from the piperazine dihydrochloride are cooled in an ice bath and treated with 25 ml. of absolute ethanol saturated at 0° with dry hydrogen chloride (Note 3). After the solution has been well mixed, it is cooled for 10–15 minutes in an ice bath. The precipitated white plates of 1-benzylpiperazine dihydrochloride are collected by suction filtration, washed with dry benzene, and dried. The product, which melts at about 280° with decomposition, after sintering at about 254° (Note 4), amounts to 29.0–29.5 g. (93–95%). A solution of this salt in 50 ml. of water is made alkaline (pH > 12) with about 60 ml. of 5*N* sodium hydroxide, then extracted twelve times with 20-ml. portions (Note 5) of chloroform. The combined extracts are dried over anhydrous sodium sulfate, and the pale-brown oil (Note 6) remaining after removal of solvent is distilled at reduced pressure in a Claisen flask. The yield of pure 1-benzylpiperazine, b.p. 122–124°/2.5 mm., n_D^{25} 1.5440–1.5450, is 14.3–16.5 g. (65–75%).

2. Notes

1. Piperazine dihydrochloride monohydrate, which is recovered almost quantitatively in this procedure, may be purchased from K and K Laboratories, Jamaica 33, New York, or from L. Light and Co., Ltd., Poyle, Colnbrook, Bucks, England. It may be readily prepared in essentially quantitative yield from the free base by the following procedure.

A brisk stream of hydrogen chloride gas is passed for 5–8 minutes into a solution of 24.3 g. (0.125 mole) of piperazine hexahydrate in 50 ml. of absolute ethanol contained in a 250-ml. Erlenmeyer flask. A wide gas-inlet tube (about 10 mm.) is used to avoid clogging, and the flask is cooled in an ice bath to keep the temperature at about 25°. After the gas stream has been discontinued, the contents of the flask are cooled to about 0°, and the crystalline product is collected by suction filtration and washed with two 25-ml. portions of ice-cold absolute ethanol. The yield is about 22 g. (0.125 mole).

2. If the filtrate from this isolation is evaporated to dryness at reduced pressure, crude 1-benzyl-4-piperazinium chloride is left as a residue. For removal of any piperazine dihydrochloride, the chloride may be crystallized after rapidly filtering a hot solution in about 50 ml. of absolute ethanol. Concentration of the filtrate, followed by cooling, gives 12.4 g. (84%) of 1-benzyl-4-piperazinium chloride as prismatic plates, m.p. 167–168°. This salt may be converted to the dihydrochloride by treatment with ethanolic hydrogen chloride.

3. When absolute ethanol is saturated with hydrogen chloride at 0°, the resultant solution is about 10.5*N* in hydrogen chloride.

4. The melting point has been reported as 253° by Baltzly and co-workers.²

5. The checkers found continuous extraction with chloroform to be convenient.

6. The free base rapidly absorbs carbon dioxide on exposure to air and should therefore be protected during both manipulation and storage. The undistilled oil may be converted in good yield to 1-benzoyl-4-benzylpiperazine hydrochloride, m.p. 245–245.5°, by treatment with benzoyl chloride in benzene solution.

3. Methods of Preparation

1-Benzylpiperazine has been prepared ^{2,3} by the reaction of piperazine and benzyl chloride, followed by fractionation of piperazine, and the mono- and dibenzyl derivatives. It has also been obtained ⁴ by alkaline hydrolysis of 1-benzyl-4-carbethoxy-piperazine. The present method, which is a modification of that first reported by Cymerman Craig, Rogers, and Tate,⁵ is simple and yields an easily purified product.

4. Merits of Preparation

The benzyl group, easily removed by hydrogenolysis, is an ideal blocking group for the preparation of 1-monosubstituted, and of 1,4-unsymmetrically disubstituted, piperazines.

Published methods for preparation of 1-benzylpiperazine involve either fractionation of mixtures of piperazine and its 1-

benzyl- and 1,4-dibenzyl derivatives or the use of 1-carbethoxy-piperazine as an intermediate. The procedure here described is simple; it yields, in 30 minutes, pure 1-benzylpiperazine dihydrochloride, stable to storage, from readily available starting materials, and free of any disubstituted compound.

¹ Department of Chemistry, University of Sydney, Sydney, Australia.

² R. Baltzly, J. S. Buck, E. Lorz, and W. Schon, *J. Am. Chem. Soc.*, **66**, 263 (1944).

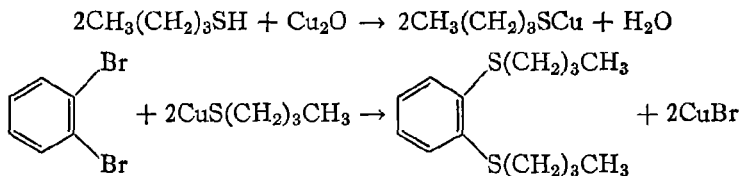
³ R. E. Lutz and N. H. Shearer, *J. Org. Chem.*, **12**, 771 (1947).

⁴ B. W. Horrom, M. Freifelder, and G. R. Stone, *J. Am. Chem. Soc.*, **77**, 753 (1955).

⁵ J. Cymerman Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.*, **9**, 397 (1956).

1,2-BIS(*n*-BUTYLTHIO)BENZENE

[Benzene, *o*-bis(butylthio)-]



Submitted by ROGER ADAMS,¹ WALTER REIFSCHNEIDER,²
and ALDO FERRETTI.³

Checked by WILLIAM E. PARHAM, WAYLAND E. NOLAND,
and JAMES R. TROCKMORTON.

1. Procedure

A. Cuprous *n*-butylmercaptide. A mixture of 42.9 g. (0.30 mole) of freshly prepared cuprous oxide (Note 1), 61.3 g. (0.68 mole) of 1-butanethiol, and 750 ml. of 95% ethanol is heated under reflux with mechanical stirring (Note 2) until the orange or red color of the cuprous oxide is completely changed to the white color of the cuprous *n*-butylmercaptide (Note 3). The product is collected by filtration, washed several times with 95%

ethanol, and dried in a vacuum. The yield is 91.6 g., essentially quantitative (Note 4).

B. *1,2-Bis(n-butylthio)benzene*. In a 1-l., round-bottomed, three-necked flask fitted with a reflux condenser, a mechanical stirrer, and a thermometer which reaches into the reaction mixture is placed a solution of 59.0 g. (0.25 mole) of *o*-dibromobenzene in a mixture of 250 ml. of quinoline and 80 ml. of pyridine. To this solution is added 84.0 g. (0.55 mole) of cuprous *n*-butylmercaptide, and the mixture is stirred and heated under reflux (Note 5) for 3.5 hours (Note 6). Heating is stopped and the reaction mixture is allowed to cool to about 100°. It is then poured into a stirred mixture of 1500 g. of ice and 400 ml. of concentrated hydrochloric acid; occasional stirring is continued for about 2 hours. The aqueous part is then decanted from the dark brown, gummy residue and is extracted twice with 400 ml. portions of ether. The ether extract is added to the residue, and the resulting mixture is stirred for about 5 minutes. The ether solution is then decanted from the residue and is filtered. The residue is extracted twice more with 400-ml. portions of ether (Note 7). The combined ether extract is washed twice with 100-ml. portions of 10% hydrochloric acid, once with water, and twice with 100-ml. portions of concentrated ammonia (Note 8). After a final wash with water, the ether solution is dried over anhydrous potassium carbonate. The potassium carbonate is collected on a filter, and the ether is removed from the filtrate by distillation. The remaining brown oil is distilled in vacuum, giving a pale orange oil, b.p. 123–124°/0.3 mm., n_D^{25} 1.5684. The yield is 46.5–56.0 g. (73–87%) (Note 9).

2. Notes

1. Cuprous oxide was prepared according to the procedure of King.⁴ A good grade of commercial cuprous oxide may also be used, but the time required to complete the conversion into mercaptide may be considerably longer (see Note 3).

2. It is not necessary to carry out the reaction under nitrogen, but it is advisable to close the condenser with a cotton plug or with a capillary tube to limit the entrance of air.

3. When freshly prepared cuprous oxide is used, a period of

about 12 hours is generally sufficient. For commercial grade cuprous oxide the time required varies between 8 and 150 hours, depending on the reactivity of the cuprous oxide.

4. The checkers obtained a yield of 97%. The submitters and checkers have found that both larger and smaller runs can be carried out without difficulty or reduction in yield.

5. The pot temperature should rise during the reaction from about 150° at the beginning of reflux to about 170° at the end of the reaction time. Pot temperatures lower than 150° and higher than 180° result in lower yields.

6. Approximately 10 minutes after the mixture starts to boil a homogeneous solution is obtained.

7. If the last ether extract is not almost colorless, one more extraction of the residue with ether should be carried out.

8. If the ammonia layer is dark blue at the second extraction, extraction with ammonia should be continued until only a pale blue extract results.

9. The present procedure has also been used by the submitters to prepare the following thioethers: 1,4-bis-(*n*-butylthio)benzene, pale yellow oil, b.p. 142°/0.5 mm., n_D^{20} 1.5726, from *p*-dibromobenzene and cuprous *n*-butylmercaptide (yield 68–74%); 1,2-bis(phenylthio)benzene, white crystals, m.p. 42.5–44.5°, b.p. 190°/1 mm., from *o*-dibromobenzene and cuprous phenylmercaptide (see below) (yield 79–83%), or from *o*-dichlorobenzene (see below) and cuprous phenylmercaptide (yield 58–71%); 1,4-bis(phenylthio)benzene, white crystals, m.p. 82–83°, from *p*-dibromobenzene and cuprous phenylmercaptide (yield 80–84%), or from *p*-dichlorobenzene (see below) and cuprous phenylmercaptide (yield 59–72%).⁶ The same method can be applied to the preparation of many other thioethers.

Cuprous phenylmercaptide is prepared from cuprous oxide and benzenethiol according to the procedure given for cuprous *n*-butylmercaptide. A heating period of only 2 hours (when freshly prepared cuprous oxide is used), however, is required to obtain the yellow compound. Chloro compounds can be used instead of bromo compounds for the reaction with cuprous phenylmercaptide. However, a higher reaction temperature (210–220°) and a longer reaction time (24 hours) is required.

The necessary pot temperature is obtained by using a mixture of 350 ml. of quinoline and 8 ml. of pyridine as solvents. It is also advantageous to use a larger excess of cuprous phenylmercaptide (121 g., 0.69 mole).

Aromatic chloro compounds cannot be used for reactions with aliphatic cuprous mercaptides.

3. Methods of Preparation

1,2-Bis(*n*-butylthio)benzene and 1,4-bis(*n*-butylthio)benzene have been prepared from the corresponding dibromobenzene and cuprous *n*-butylmercaptide, using a mixture of quinoline and pyridine as solvent.^{5,6} 1,2-Bis(phenylthio)benzene and 1,4-bis(phenylthio)benzene have been prepared from the corresponding dichloro- or dibromobenzenes and cuprous phenylmercaptide, using a mixture of quinoline and pyridine as solvent.⁵ 1,4-Bis(phenylthio)benzene has also been prepared from *p*-dibromobenzene or *p*-bromophenyl phenyl sulfide and lead phenylmercaptide⁷ and from diazotized 4-aminophenyl phenyl sulfide and sodium phenylmercaptide.⁸

4. Merits of Preparation

As indicated (Note 9), the present procedure can be adapted for the preparation of a wide range of aryl and vinyl sulfides.⁶ This, in combination with the cleavage reaction described for the preparation of 1,2-dimercaptobenzene (p. 54), provides a convenient and general method for the preparation of aryl mercaptans.

¹ University of Illinois, Urbana, Illinois.

² Agricultural Chemical Research, The Dow Chemical Co., Midland, Michigan.

³ Via Martiri Triestini, 12, Milan, Italy.

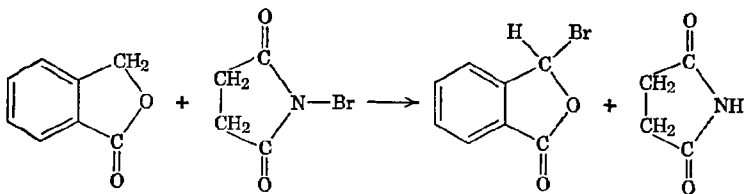
⁴ A. King, *Inorganic Preparations*, D. Van Nostrand Co., Inc., Princeton, New Jersey, 1936, p. 39.

⁵ R. Adams, W. Reifschneider, and M. D. Nair, *Croat. Chem. Acta*, **29**, 277 (1957).

⁶ R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4927 (1959).

⁷ E. Bourgeois and A. Fouassin, *Bull. soc. chim. France*, [4] **9**, 938 (1911); *Rec. trav. chim.*, **30**, 431 (1911).

⁸ G. Leandri and M. Pallotti, *Ann. chim. (Rome)*, **46**, 1069 (1956).

3-BROMOPHTHALIDE**[1(3H)-Isobenzofuranone, 3-bromo-]**Submitted by I. A. KOTEN and ROBERT J. SAUER.¹

Checked by R. C. JUOLA, MARJORIE C. CASERIO, and JOHN D. ROBERTS.

1. Procedure

Ten grams (0.075 mole) of phthalide (Note 1), 13.3 g. (0.075 mole) of N-bromosuccinimide (Note 1), and 200 ml. of dry carbon tetrachloride (Note 1) are refluxed for 30 minutes in a 500-ml. flask carrying a reflux condenser equipped with a drying tube containing Drierite. The reaction mixture is exposed to the light of an ordinary 100-watt unfrosted light bulb placed 6-8 in. from the flask. The end of the reaction is indicated by the disappearance of N-bromosuccinimide from the bottom of the flask and accumulation of succinimide at the top of the reaction mixture. The succinimide is removed by filtration and the filtrate concentrated under atmospheric pressure to 15-20 ml. Cooling of this concentrate followed by filtration gives 12-13 g. (75-81%) of crude 3-bromophthalide, m.p. 74-80°. The crude material, when recrystallized from cyclohexane, gives colorless plates, m.p. 78-80° (Notes 2-4).

2. Notes

1. The phthalide used was obtained from Aldrich Chemical Co. It was also prepared by the method of Gardner and Naylor, *Org.*

Syntheses Coll. Vol. 2, 526 (1943). The N-bromosuccinimide was obtained from Arapahoe Chemicals, Inc.

The carbon tetrachloride used is dried over Drierite and filtered or distilled.

2. About 150 ml. of cyclohexane is necessary to recrystallize 12–13 g. of product, and the temperature of the solvent should be kept below 70° to avoid oiling of undissolved material. The recovery is 11–12 g.

3. When pure 3-bromophthalide is allowed to stand, its melting point is depressed, owing apparently to some decomposition. It may, therefore, be desirable to prepare the compound in smaller quantities than specified here. A sample of 3-bromophthalide, prepared by using 20 g. of phthalide and 26.6 g. of N-bromosuccinimide, amounted to 29.8 g. (93.4%) of crude product. Hydrolysis of the crude material² gave phthalaldehydic acid, m.p. 96–98°.

4. Since one of the checkers developed a serious allergy to 3-bromophthalide, suitable precautions should be taken to avoid its inhalation and contact with the skin.

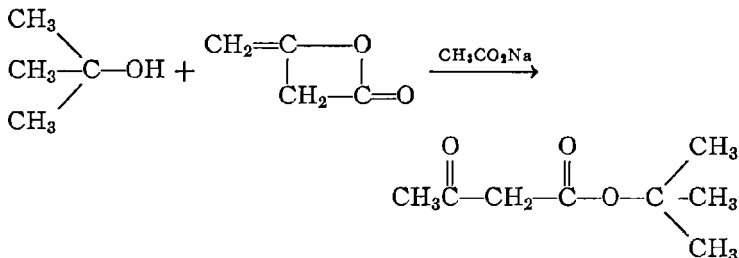
3. Methods and Merits of Preparation

3-Bromophthalide has previously been prepared by direct bromination of phthalide over a period of 10–13 hours in yields of 82–83%.² The procedure above, a modification of the Wohl-Ziegler method, appears to be preferable since it may be completed in 3–4 hours, is applicable to the preparation of small samples, and gives comparable yields.

¹ Department of Chemistry, North Central College, Naperville, Ill. This work was supported by a grant from Research Corporation of New York City.

² R. L. Shriner and F. J. Wolf, *Org. Syntheses Coll. Vol. 3*, 737 (1955).

***tert*-BUTYL ACETOACETATE**
(Acetoacetic acid, *tert*-butyl ester)



Submitted by SVEN-OLOV LAWESSON, SUSANNE GRONWALL, and
RUNE SANDBERG.¹

Checked by WILLIAM G. DAUBEN and RICHARD ELLIS.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to diketene, which is toxic and which may irritate mucous tissues such as those of the eyes; the use of safety goggles is recommended.

A 500-ml. three-necked flask is equipped with a sealed mechanical stirrer, a dropping funnel, and a two-armed addition tube, one arm of which bears a reflux condenser and the other arm of which is fitted with a thermometer. *tert*-Butyl alcohol (79 g., 1.07 moles) (Note 1) is added to the flask and the thermometer arranged so that its bulb is immersed in the liquid but out of the path of the stirrer. The flask is heated by means of an electric mantle until the temperature of the liquid is 80–85°, and the mantle then is removed. Anhydrous sodium acetate (0.4 g., 4.8 mmoles) is added with stirring, and then 96 g. (1.14 moles) of diketene (Note 2) is added dropwise over a period of 2.5 hours. The temperature of the solution drops to 60–70° during the first 15 minutes and then increases slowly to 110–115°. When all the

diketene is added, the reaction subsides and, after the resulting brown-black solution is stirred for an additional 30 minutes, the product is distilled immediately under reduced pressure through a short column. After a small fore-run, the yield of *tert*-butyl acetoacetate, b.p. 85°/20 mm. (Note 3), n_D^{20} 1.4200–1.4203, is 127–135 g. (75–80%) (Note 4).

2. Notes

1. Eastman Kodak white label grade is used without further purification.

2. The submitters used material directly as supplied by Dr. Theodor Schuchardt and Co., Munich, Germany. The checkers used material directly as supplied by Aldrich Chemical Co., Milwaukee, Wisconsin.

3. The still residue is dehydroacetic acid.

4. In a run five times the size described, the submitters report that the reaction goes in the same manner and in 85–92% yield.

3. Methods of Preparation

tert-Butyl acetoacetate has been prepared by self-condensation of *tert*-butyl acetate.^{2,3} The described procedure is based upon the method of Treibs and Hintermeier.⁴

4. Merits of Preparation

This preparation is illustrative of a general method of preparing esters of acetoacetic acid. It is particularly useful because the starting materials are easily accessible and the yields are high.

¹ Present address: Department of Organic Chemistry, Aarhus University, Aarhus, Denmark.

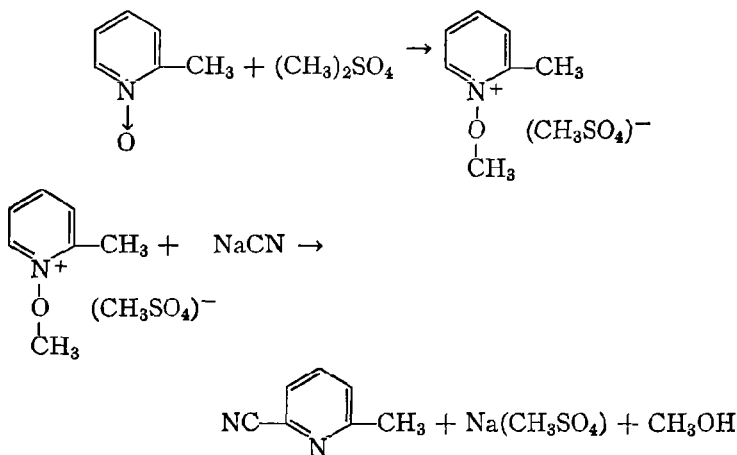
² N. Fisher and S. M. McElvain, *J. Am. Chem. Soc.*, **56**, 1766 (1934).

³ W. B. Renfrow and G. B. Walker, *J. Am. Chem. Soc.*, **70**, 3957 (1948).

⁴ A. Treibs and K. Hintermeier, *Chem. Ber.*, **87**, 1163 (1954).

2-CYANO-6-METHYLPYRIDINE

(6-Methylpicolinonitrile)



Submitted by WAYNE E. FEELY, GEORGE EVANEGA,
and ELLINGTON M. BEAVERS.¹

Checked by WILLIAM E. PARHAM, STUART W. FENTON,
and WILLIAM W. HENDERSON.

1. Procedure

Caution! All the operations should be carried out in a well-ventilated hood because of the toxic natures of dimethyl sulfate, hydrogen cyanide, and cyanide solutions.

A. *1-Methoxy-2-methylpyridinium methyl sulfate.* In a 1-l. three-necked flask equipped with a Hirshberg stirrer, a thermometer which extends deep into the flask, and a 250-ml. pressure-equalizing, dropping funnel fitted with a calcium chloride drying tube is placed 109 g. (1.0 mole) of dry powdered 2-picoline-1-oxide (Note 1). The stirrer is started at a slow rate, and 126 g. (1.0 mole) of dimethyl sulfate (Note 2) is added dropwise at a

rate such that the temperature of the reaction mixture slowly rises to between 80° and 90° and remains in this range throughout the addition (Note 3). When the addition is about two-thirds complete, gentle heating with a steam bath is necessary to maintain this temperature. After complete addition (about 1 hour), the mixture is heated for an additional 2 hours on a steam bath at 90–100°. The molten salt is then poured into a large evaporating dish and placed in a vacuum desiccator under partial vacuum to cool. The salt is obtained as a white crystalline mass in essentially quantitative yield (235 g.) (Notes 4 and 5).

B. *2-Cyano-6-methylpyridine*. In a 2-l., three-necked, round-bottomed flask equipped with a Hershberg stirrer, a 500-ml. pressure-equalizing, dropping funnel without a stopper, and a thermometer-gas inlet adapter (Note 6) fitted with a thermometer which reaches deep into the flask is placed a solution of 147 g. (3.0 mole) of sodium cyanide dissolved in 400 ml. of water. The stirrer is started and the apparatus is flushed with prepurified nitrogen for 1 hour (Note 7). The solution in the flask is then cooled to 0° with an ice bath, and a solution of 235 g. (1.0 mole) of 1-methoxy-2-methylpyridinium methyl sulfate dissolved in 300 ml. of water is added dropwise over a period of 2 hours. The dropping funnel and the thermometer-adapter are then quickly removed and replaced by stoppers, and the flask is allowed to stand in a refrigerator overnight (12–16 hours). The flask, containing needles of the crude nitrile (Note 8), is removed from the refrigerator and the contents stirred at room temperature for 6 hours. After addition of 200 ml. of chloroform, the contents of the flask are transferred to a large separatory funnel and the layers separated. Extraction of the aqueous phase is repeated twice with 100-ml. portions of chloroform, and the combined extracts are dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the filtrate is concentrated on a steam bath to remove chloroform, and the residual crude cyanopicoline (90–110 g.) is transferred, while hot, to a distilling flask. Distillation under reduced pressure (30 mm.) (Note 9) gives three fractions: Fraction I, b.p. 99–106°, weighs 15–20 g.; Fraction II, b.p. 106–124°, weighs 5–10 g.; and Fraction III, b.p. 125–131°, weighs 60–70 g. (Note 10). Fraction III is

dissolved in 1 l. of hot 10% ethyl alcohol, treated with 0.5 g. of activated carbon, filtered, and the filtrate is allowed to cool slowly to room temperature. The 2-cyano-6-methylpyridine separates as white prismatic needles, m.p. 71–73°, and weighs 48–54 g. (40–46% based on 2-picoline-1-oxide) (Notes 11 and 12).

2. Notes

1. The preparation of 2-picoline-1-oxide is described by Boekelheide and Linn.² The oxide is hygroscopic, and best results are obtained if it is redistilled just before use. The submitters used 2-picoline-1-oxide, obtained from the Reilly Tar and Chemical Company, Indianapolis, Indiana, which was freshly redistilled and boiled at 118–120°/10 mm.

2. Eastman Kodak Company practical grade was used. Dimethyl sulfate is toxic and must be handled with caution. Provision should be made for containing the contents should breakage occur. Ammonia is a specific antidote for dimethyl sulfate and should be at hand to destroy any accidentally spilled.

3. The submitters have observed that, when 1-methoxy-pyridinium methyl sulfate salts are heated above about 140–150°, violent explosions usually result.

4. The salt is very hygroscopic. Aqueous solutions of the salt slowly hydrolyze upon standing to di(1-methoxy-2-methylpyridinium) sulfate but may be used in the subsequent step without adverse effects.

5. The salt may be recrystallized from anhydrous acetone, giving colorless prisms, m.p. 67–70°.³

6. A thermometer adapted with a gas-addition tube may be purchased from Ace Glass Inc., Vineland, New Jersey (Cat. No. 5266).

7. The presence of small amounts of air during the formation of the nitrile rapidly darkens the reaction mixture.

8. The crude 2-cyano-6-methylpyridine which has separated (40–50 g.) may be recrystallized from dilute ethyl alcohol to yield 35–45 g. of pure product.

9. The distillation is conveniently performed in a Claisen flask with a fractionating side arm. The checkers used a heat lamp to prevent solidification of product in the condenser.

10. Fraction I, b.p. 99–106°/30 mm., is mostly 4-cyano-2-methylpyridine and is best purified by redistillation.⁴ Fraction II, b.p. 106–125°/30 mm., contains a mixture of the two nitriles and may be further purified by redistillation.

11. Physical constants reported for 2-cyano-6-methylpyridine are b.p. 135–136°/38 mm.,⁵ m.p. 69–71°,⁵ m.p. 72–74°.^{6,7}

12. This general method has been used to prepare 2- and 4-cyanopyridine from pyridine-1-oxide in 32% and 49% yields, respectively; 2-cyano-4,6-dimethylpyridine (73%) from 4,6-dimethylpyridine-1-oxide; 2-cyanoquinoline (93%) from quinoline-1-oxide; and 1-cyanoisoquinoline (95%) from isoquinoline-2-oxide.⁸

3. Methods of Preparation

The present method is essentially that given by Feely and Beavers.³ 2-Cyano-6-methylpyridine also has been prepared by the fusion of sodium 6-methylpyridine-2-sulfonate with potassium cyanide.⁵ In addition, this nitrile has been prepared from 2-chloro 6 methylpyridine ⁶ (no yield stated) and from a catalytic reaction of 2,6-lutidine with air and ammonia in low yield.^{6,7}

4. Merits of Preparation

This preparation describes a convenient and general method for preparing cyano derivatives of pyridine, quinoline, and isoquinoline from the corresponding, and readily available, amine oxides.

¹ Research Laboratories, Rohm and Haas Co., Philadelphia, Pennsylvania.

² V. Bockelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

³ W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959).

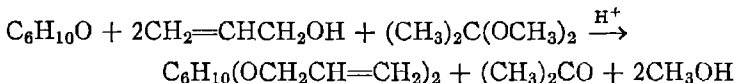
⁴ E. Ochiai and I. Suzuki, *Pharm. Bull. (Tokyo)*, **2**, 247 (1954).

⁵ I. Suzuki, *Pharm. Bull. (Tokyo)*, **5**, 13 (1957).

⁶ G. Mayurnik, A. F. Moschetto, H. S. Block, and J. V. Scudi, *Ind. Eng. Chem.*, **44**, 1630 (1952).

⁷ Pyridium Corp., Brit. pat. 671,763 [*C. A.*, **47**, 1746 (1953)].

CYCLOHEXANONE DIALLYL ACETAL



Submitted by W. L. HOWARD and N. B. LORETTE.¹

Checked by E. J. COREY and R. A. E. WINTER.

1. Procedure

A solution of 294 g. (3 moles) of cyclohexanone, 343 g. (3.3 moles) of acetone dimethyl acetal, 418 g. (7.2 moles) of allyl alcohol, 1 l. of benzene, and 0.2 g. of *p*-toluenesulfonic acid monohydrate (Note 1) is distilled using a good fractionating column until the acetone and the benzene-methanol azeotrope are completely removed (Note 2). The solution is cooled below the boiling point, and a solution of 0.5 g. of sodium methoxide in 20 ml. of methanol is added all at once with stirring (Note 3). Distillation is resumed, and unreacted allyl alcohol and benzene are removed at atmospheric pressure and then at reduced pressure (Note 4). Distillation is continued at a pressure in the range 5–20 mm. to remove forerun (on the order of 100 ml.) (Note 5). The cyclohexanone diallyl acetal, b.p. 84°/5 mm., 98°/10 mm., 114°/20 mm., n_D^{25} 1.4600, is then collected. The yield is 382–435 g. (65–74%). A small amount of higher-boiling residue remains.

2. Notes

1. Commercial acetone dimethyl acetal and allyl alcohol from The Dow Chemical Company and cyclohexanone from Eastman Kodak Company were used without further treatment.

2. These reaction products distil within a narrow range. The head temperature was maintained in the range 56–59°. About 750 ml. of distillate is collected, depending on the efficiency of fractionation. The combined amount of methanol and acetone

may be estimated by washing an aliquot of the distillate with 2 volumes of water and taking the difference between the original volume and that of the residual benzene as the volume of methanol-acetone. Usually this is about 450 ml. The distillation should be as rapid as possible to avoid the formation of by-product 2-allylcyclohexanone. A 1.9 x 120 cm. vacuum-jacketed, silvered column packed with 0.25-in. glass helices and fitted with a vapor-dividing head controlled by a timed relay was used.

The checkers used a 1.3 x 92 cm. vacuum-jacketed, silvered column packed with 0.25-in. glass ring chains. With this column it was necessary to carry out the distillation of benzene-acetone-methanol using reflux ratios varying from 2:1 initially to 11:1 at the conclusion. The use of a shorter column is not satisfactory.

3. Other soluble, non-volatile bases may be used to neutralize the acid. The reactants may be kept at room temperature safely after addition of base.

4. An azeotrope of benzene and allyl alcohol distils at about 77°, followed by benzene. When the temperature in the boiling flask reaches 120–130°, the pressure is reduced and the remaining benzene is taken to a cold trap.

5. The forerun contains some acetone diallyl acetal and about 35–40 g. of 2-allylcyclohexanone, b.p. 78°/10 mm.

3. Methods of Preparation

Cyclohexanone diallyl acetal has been prepared from cyclohexanone and allyl orthosilicate² and by the above procedure.³

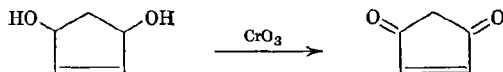
4. Merits of Preparation

The preparation given here is operable for a large number of ketone acetals, including those formed from both primary and secondary alcohols and from alcohols and ketones containing other functional groups which are stable under the conditions used.³

¹ The Dow Chemical Company, Texas Division, Freeport, Texas.

² B. Helferich and J. Hausen, *Ber.*, **57B**, 795 (1924) [*C. A.*, **18**, 2869 (1924)].

³ N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

2-CYCLOPENTENE-1,4-DIONE

Submitted by GARY H. RASMUSSEN,¹ HERBERT O. HOUSE,¹
EDWARD F. ZAWESKI,² and CHARLES H. DEPUY.²

Checked by WILLIAM G. DAUBEN, PHILIP E. EATON, and
RICHARD SCHNEIDER.

1. Procedure

In a 2-l. three-necked flask equipped with a thermometer, a mechanical stirrer, and a dropping funnel (Note 1) is placed a mixture of 45.1 g. (0.45 mole) of a dihydroxycyclopentene mixture (Note 2), 200 ml. of water, and 300 ml. of methylene chloride. After this mixture has been cooled to -5° to 0° by means of an external cooling bath (Note 3), the addition of a solution of 100 g. (1.0 mole) of chromium trioxide and 160 ml. of concentrated sulfuric acid in 450 ml. of water is begun. The solution of the oxidant is added dropwise, and with stirring, at such a rate that the temperature of the reaction mixture remains between -5° and 0° . After the addition is complete (Note 4), the mixture is stirred at -5° to 0° for 1 hour and then 200 ml. of chloroform is added. The resulting mixture is stirred for 10 minutes, the organic layer is separated, and then the aqueous layer is extracted with two 200-ml. portions of a mixture (1:1 by volume) of chloroform and methylene chloride. The combined organic extracts are washed with 100 ml. of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at room temperature. The yield of 2-cyclopentene-1,4-dione (Note 5), which crystallizes as yellow plates melting at 30.0 – 32° , is 17–22 g. (39–50% based on the dihydroxycyclopentene mixture) (Note 6).

2. Notes

1. All glassware must be washed with acid before use.
2. The dihydroxycyclopentene mixture was prepared from cyclopentene and peracetic acid.³ The mixture contains approximately 70% of 2-cyclopentene-1,4-diol.
3. The submitters found a cooling bath composed of a Dry Ice and methanol-water mixture (1:3 by volume) to be convenient.
4. At this point in the preparation, an excess of the oxidant should be present. The presence of excess oxidant may be established by diluting 2 drops of the aqueous phase from the reaction mixture with 2 ml. of water and then adding 1 drop of a 0.4% solution of sodium diphenylaminesulfonate in water. A deepening in color is observed if excess oxidant is present.
5. This product is sufficiently pure for most applications. Further purification may be achieved either by sublimation of the product at 30–40°/0.1 mm. or by recrystallization of the dione from diethyl ether at Dry Ice temperatures. The dione decomposes rapidly at temperatures above 40°. An ethanol solution of pure dione, m.p. 35–36°, exhibits a maximum in the ultraviolet at 222 μ ($\log \epsilon$ 4.16).
6. Starting with pure 2-cyclopentene-1,4-diol, the submitters obtained the dione in 67–79% yield.

3. Methods of Preparation

2-Cyclopentene-1,4-dione has been prepared by oxidation of 2-cyclopentene-1,4-diol with chromium trioxide in aqueous acetic acid^{4,5} or in aqueous acetone,⁴ and with silver chromate.⁶ The present method eliminates the tedious removal of large amounts of acetic acid and gives a higher yield.

4. Merits of Preparation

2-Cyclopentene-1,4-dione is a very reactive dienophile in the Diels-Alder reaction and thus provides access to a variety of compounds containing the reactive β -dicarbonyl grouping in a five-

membered ring.⁴ Also, its multiple functionality makes it a versatile starting material for other types of reactions as well.

¹ Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.

² Department of Chemistry, Iowa State University, Ames, Iowa.

³ M. Kovach, D. R. Nielsen, and W. H. Rideout, this volume, p. 50.

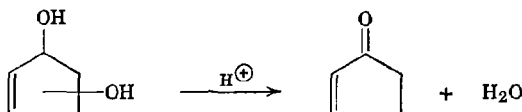
⁴ C. H. DePuy and E. F. Zaweski, *J. Am. Chem. Soc.*, **81**, 4920 (1959).

⁵ V. F. Kucherov and L. I. Ivanova, *Doklady Akad. Nauk S.S.S.R.*, **131**, 1077 (1960); [*C. A.*, **54**, 21021 (1960)].

⁶ E. Y. Gren and G. Vanags, *Doklady Akad. Nauk S.S.S.R.*, **133**, 588 (1960); [*C. A.*, **54**, 24442 (1960)].

2-CYCLOPENTENONE

(2-Cyclopentene-1-one)



Submitted by CHARLES H. DEPUY and K. L. EILERS.¹

Checked by WILLIAM G. DAUBEN, ROBERT A. FLATH,
and GILBERT H. BEREZIN.

1. Procedure

In a 250-ml. round-bottomed flask fitted for vacuum distillation with a short path distilling head (Note 1), a condenser, and a 250-ml. receiving flask is placed 100 g. (1.0 mole) of a mixture of cyclopentenediols.² A few Carborundum boiling chips are added. The receiver is cooled in ice and the mixture heated to 50–55° (Note 2). At this time, the flask is opened momentarily and 1–2 g. of *p*-toluenesulfonic acid monohydrate is added. The flask is immediately closed and the pressure is reduced to 10–15 mm. Careful heating is continued, and a mixture of 2-cyclopentenone and water begins to distil with the temperature in the distilling head rising from 45° to 60° (Note 3). The temperature of the flask is gradually increased as necessary to maintain a reasonably rapid distillation rate.

The reaction is complete when approximately 10% of the original material remains in the distilling flask. The distillation normally requires 30–60 minutes.

The distillate, containing 2-cyclopentenone, water and varying amounts of cyclopentenediols, is dissolved in 150 ml. of methylene chloride and dried over anhydrous sodium sulfate. The solvent is carefully removed through a Vigreux column and the residue purified by distillation. After a forerun (b.p. 50–150°), there is collected 44–49 g. (53–60%) of pure 2-cyclopentenone, b.p. 151–154°. Cyclopentenediols may be recovered from the pot residue by distillation at 0.1 mm. The forerun contains appreciable amounts of cyclopentenone and should be added to a succeeding preparation before final distillation.

2. Notes

1. The distilling head should be short and unobstructed, for any attempt at fractionation at this stage leads to resinification of the 2-cyclopentenone by the acid. No capillary bleed is used, since the product is extremely sensitive to oxygen.

2. The submitters have found a 250-watt infrared heat lamp controlled by a Variac to be the most convenient source of heat. Occasionally, the reaction may become rapid and exothermic, and it is important to remove the heat source as quickly as possible. If an oil bath is used, the temperature is gradually increased until it approaches 150° at the end of the reaction.

3. If the temperature of the distillate rises much above 60° at this pressure, considerable amounts of diols co-distil and the yield of 2-cyclopentenone is diminished. If a reasonably rapid distillation does not occur with a head temperature below 60°, an additional gram of acid should be added after lowering the temperature of the distillation flask below 50°.

3. Methods of Preparation

Previous preparations of 2-cyclopentenone have involved the elimination of HCl from 2-chlorocyclopentanone³ or its ketal.⁴ The oxidation of 3-chloro-⁵ or 3-hydroxycyclopentene⁶ has been

utilized as well as the direct oxidation of cyclopentene with H_2O_2 .⁷ Cyclopentenone has also been prepared from 1-dicyclopentadienol.⁸

4. Merits of Preparation

The α,β -unsaturated ketone system in 2-cyclopentenone makes possible a wide variety of reactions of the Michael and Diels-Alder type. Thus 2-cyclopentenone is a versatile starting material for preparing compounds containing a five-membered ring. The availability of the dihydroxycyclopentene mixture (p. 50) makes the present procedure the method of choice for its preparation.

¹ Department of Chemistry, Iowa State University, Ames, Iowa.

² M. Kovach, D. R. Nielsen, and W. H. Rideout, this volume, p. 50.

³ E. J. Corey and K. Osugi, *Pharm. Bull. (Tokyo)*, **1**, 99 (1953).

⁴ H. Wanzlick, G. Gollmer, and M. Milz, *Ber.*, **88**, 69 (1955).

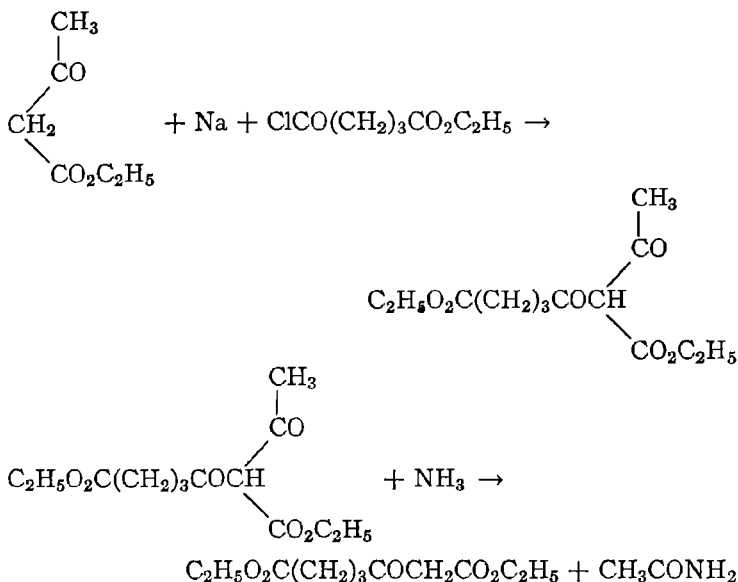
⁵ K. Alder and F. H. Flock, *Ber.*, **89**, 1732 (1956).

⁶ E. Dane and K. Eder, *Ann.*, **539**, 207 (1939).

⁷ W. Treibs, G. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

⁸ M. Rosenblum, *J. Am. Chem. Soc.*, **79**, 3179 (1957).

DIETHYL β -KETOPIMELATE
(Pimelic acid, β -oxo-, diethyl ester)



Submitted by MAYA GUHA and D. NASIPURI.¹

Checked by WILLIAM G. DAUBEN and RICHARD ELLIS.

1. Procedure

A. *Diethyl α -acetyl- β -ketopimelate*. In a 2-l. three-necked flask equipped with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected with a calcium chloride tube are placed 11.5 g. (0.5 g. atom) of finely powdered sodium (Note 1) and 500 ml. of dry ether. The flask is placed in an ice bath, and 65.0 g. (63.5 ml., 0.5 mole) of freshly distilled ethyl acetoacetate in 150 ml. of dry ether is slowly added from the dropping funnel with stirring (approximate time for addition is 30–40 minutes). The mixture is stirred overnight, then it is

cooled in an ice bath, and 89.0 g. (0.5 mole) of γ -carbethoxybutyryl chloride (Note 2) in 200 ml. of dry ether is added gradually over the course of 1 hour. The reaction is first stirred overnight at room temperature, then gently refluxed by heating in a water bath for 30 minutes. The mixture is cooled in an ice bath, and a cold solution of 20 ml. of concentrated sulfuric acid in 300 ml. of water is added cautiously with vigorous stirring. The stirring is continued until two clear layers form when the stirring is stopped. The ethereal layer is separated and the aqueous layer extracted once with 100 ml. of ether. The two organic layers are combined, washed once with water, and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed by heating the ethereal solution on a water bath held at about 50–60°. The residual light-brown liquid is transferred to a 150 ml. Claisen flask and distilled under reduced pressure. The fraction boiling at 142–147°/0.4 mm. or 158–162°/2.5 mm. is collected (Note 3). The yield is 84–91 g. (61–66%), n_D^{28} 1.4649–1.4655.

B. *Diethyl β -ketopimelate*. In a 250-ml. distillation flask fitted with an inlet tube reaching near the bottom of the flask and a soda-lime drying tube on the side-arm is placed a solution of 50 g. (0.18 mole) of diethyl α -acetyl- β -ketopimelate in 75 ml. of dry ether. The solution is cooled by placing the flask in an ice-salt bath, and then a slow stream of ammonia gas is passed through the inlet tube. The solution becomes turbid during the first few minutes and soon becomes clear again. The gas stream is continued for 45–50 minutes, and the yellow liquid is allowed to stand at room temperature overnight with due protection from atmospheric moisture. Most of the ether is then removed by passing a stream of dry air through the solution, and the residue is transferred to a separatory funnel with the aid of 50 ml. of ether. The ethereal solution is washed with three 70-ml. portions of cold 3*N* hydrochloric acid, each extraction being shaken vigorously for 10 minutes. The ethereal layer is set aside, and the acid washings are extracted twice with 50-ml. portions of ether. The combined ethereal extracts are washed once with water and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed by heating

the solution on a water bath. The residue is transferred to a Claisen flask with a short Vigreux column, and the fraction boiling at 130–132°/0.5 mm. or 120–121°/0.2 mm. is collected (Notes 4 and 5). The yield is 21–25 g. (50–59%), n_D^{28} 1.4400, $n_D^{31.5}$ 1.4376, $n_D^{36.5}$ 1.4338.

2. Notes

1. Clean pieces of sodium are melted under xylene and powdered by vigorous shaking. When cold, the xylene is decanted and the sodium powder is washed by decantation with a few milliliters of dry ether and then washed into the reaction flask with dry ether.

2. The γ -carbethoxybutyryl chloride (b.p. 100–101°/5–6 mm. or 108–110°/15 mm.) was prepared by the method of Bachmann, Kushner, and Stevenson.²

3. The distillate contains mostly C-acyl ester with a little of O-acyl ester. Separation of these two esters by means of a carbonate solution in which only the C-acyl ester is soluble^{3,4} is possible. This separation is unnecessary in the present procedure for the O-acyl derivative gives rise to ethyl acetoacetate during decomposition with ammonia. This low-boiling ester is removed during the distillation of diethyl β -ketopimelate.

4. A small fore-run, b.p. 60–80°/5 mm., is collected which gives a positive test with ferric chloride reagent. Presumably this fraction consists mostly of ethyl acetoacetate.

5. The checkers used an 18-in. Vigreux column with a heated jacket and observed a boiling point of 126–128°/2 mm.

3. Methods of Preparation

The described method of preparing diethyl β -ketopimelate is a modification of that described by Bouveault⁵ and is essentially the same as that reported by Bardhan and Nasipuri.⁶ This ester has also been prepared by condensation of γ -carbethoxybutyryl chloride with ethoxymagnesiummalonic ester and cleavage of the resulting acylated malonic ester by β -naphthalenesulfonic acid⁷ or by acetic or propionic acids containing a trace of concentrated sulfuric acid.⁸

4. Merits of Preparation

The present method offers a more convenient synthesis with appreciably higher yields of diethyl β -ketopimclate. It is reported to be useful for the preparation of dimethyl β -ketoadipate^{8,9} and diethyl β -ketosubcrate.⁴

¹ Department of Chemistry, University of Calcutta, Calcutta 9, India.

² W. E. Bachmann, S. Kushner, and A. C. Stevenson, *J. Am. Chem. Soc.*, **64**, 974 (1942).

³ J. C. Bardhan, *J. Chem. Soc.*, **1936**, 1848.

⁴ S. Archer and G. Pratt, *J. Am. Chem. Soc.*, **66**, 1656 (1944).

⁵ L. Bouveault, *Compt. rend.*, **131**, 45 (1900).

⁶ J. C. Bardhan and D. Nasipuri, *J. Chem. Soc.*, **1956**, 350.

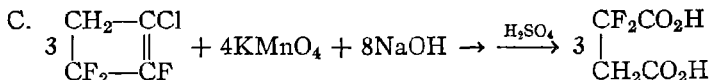
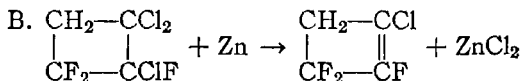
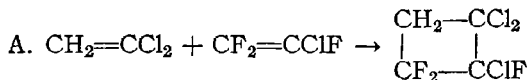
⁷ J. H. Hunter and J. A. Hogg, *J. Am. Chem. Soc.*, **71**, 1922 (1949).

⁸ H. J. E. Loewenthal, *J. Chem. Soc.*, **1953**, 3962; R. E. Bowman, *J. Chem. Soc.*, **1950**, 322.

⁹ J. Korman, *J. Org. Chem.*, **22**, 849 (1957).

2,2-DIFLUOROSUCCINIC ACID

(Succinic acid, 2,2-difluoro-)



Submitted by M. S. RAASCH and J. E. CASTLE.¹

Checked by R. H. ULOTH and R. R. COVINGTON.²

1. Procedure

Caution! In the absence of toxicity data, the fluorine compounds should all be treated as though they were toxic materials.

A. *1,1,2-Trichloro-2,3,3-trifluorocyclobutane*. In a 1-l. rocker bomb are placed 350 g. (3.6 moles) of 1,1-dichloroethylene (Note 1) and 1 g. of hydroquinone. The bomb is cooled in a mixture of Dry Ice and acetone and evacuated. The vacuum is released with nitrogen and the bomb is again evacuated. The bomb is then charged with 300 g. (2.6 moles) of chlorotrifluoroethylene (Note 1) from a cylinder. The bomb is heated at 180° for 7 hours behind a barricade (Note 2) and is then cooled, vented, and unloaded. The solid polymer (about 45 g.) is removed by filtration and is rinsed with 50 ml. of ether. The combined filtrate and rinse are concentrated and then distilled through a 30-cm. packed column to give 242–262 g. (44–48%) of 1,1,2-trichloro-2,3,3-trifluorocyclobutane, b.p. 120–121°, n_D^{25} 1.4139–1.4141.

B. *1-Chloro-2,3,3-trifluorocyclobutene*. A 1-l. three-necked flask fitted with mercury-sealed stirrer, dropping funnel, reflux condenser, and heater is charged with 150 ml. of absolute ethyl alcohol and 76 g. (1 mole) of 95% zinc dust. The alcohol is heated to boiling, and 235 g. (1.1 moles) of 1,1,2-trichloro-2,3,3-trifluorocyclobutane is added through the dropping funnel during 40 minutes. After the reaction has started, external heating is decreased. The mixture is heated under reflux for 1 hour after the end of the addition. It is then cooled below reflux temperature, 15 g. (0.2 mole) more of zinc powder is added, and the heating under reflux is continued for 30 minutes more. The mixture is again cooled below reflux temperature, and a simple still head arranged for downward distillation is attached in place of the condenser. Distillation is carried out until 165 ml. of distillate has been collected. The still head reaches a temperature of about 90°. The distillate is washed with two 250-ml. portions of water and dried by shaking gently for 5 minutes with 5 g. of 8-mesh calcium chloride. The product is decanted from the calcium chloride and distilled through a 30-cm. packed column to give 107–113 g. (68–72%) of 1-chloro-2,3,3-trifluorocyclobutene, b.p. 52–53°, n_D^{25} 1.3614–1.3619.

C. *2,2-Difluorosuccinic acid*. In a 3-l. three-necked flask fitted with stirrer, thermometer, and dropping funnel, 80 g. (2 moles) of sodium hydroxide is dissolved in 2 l. of water and 158 g. (1 mole) of potassium permanganate is then added. The mixture

is cooled to 15–20° with an ice-salt bath, and 107 g. (0.75 mole) of 1-chloro-2,3,3-trifluorocyclobutene is added through the dropping funnel during 1 hour while the permanganate solution is stirred and maintained at 15–20°. After the solution has been stirred for 2 hours more at this temperature, the manganese dioxide is removed by filtration and rinsed with three 300-ml. portions of water. The combined filtrate and washings are concentrated to a volume of 500 ml. by evaporation on a steam bath (Note 3). The solution is then cooled and 85 ml. of concentrated sulfuric acid is added slowly with stirring. The cold solution is extracted with four 250-ml. portions of ether (Note 4). Drying of the ether extract is accomplished by agitating it for 5 minutes with 30 g. of anhydrous magnesium sulfate. When the drying agent has been removed by filtration and rinsed with ether, the filtrate and the ether washings are combined and concentrated to give 91–97 g. (79–84%) of 2,2-difluorosuccinic acid. The acid is recrystallized by dissolving it in hot nitromethane (1.25 ml. per g.), filtering the solution through a layer of filter aid if necessary, and cooling the solution to 3°. The crystals are collected by suction filtration and rinsed with 30 ml. of cold nitromethane. After drying, this gives 85–92 g. (74–80%) of 2,2-difluorosuccinic acid, m.p. 144–146°.

2. Notes

1. The checkers employed 1,1-dichloroethylene supplied by Dow Chemical Co., Midland, Michigan, and chlorotrifluoroethylene supplied by the Matheson Company, Joliet, Illinois.

2. This reaction has been carried out many times without incident in a 1-l. stainless steel rocker bomb. A pressure gauge was attached during two runs and recorded a maximum of 750 p.s.i. However, an attempt in another laboratory to scale up the reaction using a 3-l. autoclave resulted in a bulged vessel. Uncontrolled polymerization may be hazardous.

3. Evaporation may be carried out in porcelain or glass dishes, but the fluoride present will cause some etching.

4. The amounts removed in the third and fourth extractions are about 5.4 g. and 1.5 g., respectively.

3. Methods of Preparation

The procedure described is the method of Raasch ^{3,4} and is the only one published so far.

4. Merits of Preparation

The first step illustrates a very general reaction, the addition of fluoroalkenes to alkenes to give fluorocyclobutanes.⁵ The subsequent steps illustrate the synthetic possibilities of fluorocyclobutanes as intermediates. 1,1,2-Trichloro-2,3,3-trifluorocyclobutane may also be converted into chlorotrifluorosuccinic acid, trifluorosuccinic acid, fluoromaleic acid, fluorofumaric acid, difluoromaleic acid, and difluorofumaric acid.^{4,5}

¹Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

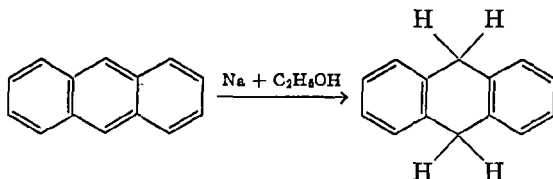
²Mead Johnson Research Center, Evansville, Indiana.

³M. S. Raasch, U. S. pat. 2,824,888 [C. A., **52**, 12901 (1958)].

⁴M. S. Raasch, R. E. Miegel, and J. E. Castle, *J. Am. Chem. Soc.*, **81**, 2678 (1959).

⁵D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *J. Am. Chem. Soc.*, **71**, 490 (1949); J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 1 (1962).

⁶M. S. Raasch, U. S. pat. 2,891,968 [C. A., **54**, 1323 (1960)].

9,10-DIHYDROANTHRACENE**(Anthracene, 9,10-dihydro-)**Submitted by K. C. BASS.¹

Checked by VIRGIL BOEKELEIDE and S. T. YOUNG.

1. Procedure

In a 2-l., three-necked, round-bottomed flask fitted with a rubber-tube sealed mechanical glass stirrer, a reflux condenser (Note 1), and a thermometer reaching to the bottom of the flask are placed 50 g. (0.28 mole) of anthracene (Note 2) and 750 ml. of commercial absolute ethanol. The suspension obtained is stirred and heated (Note 3) to 50°, and 75 g. (3.25 g. atom) of freshly cut sodium is added in quantities of about 10 g. each to the stirred mixture over a period of 5 minutes. The reaction mixture boils vigorously (Note 4) and stirring is continued for 15 minutes longer. The reaction mixture is then cooled and carefully diluted with 1 l. of water. The white-yellow solid which separates is a mixture of 9,10-dihydroanthracene and anthracene, and it is collected on a Büchner funnel, washed with 400 ml. of water, and dried in air.

The dry white-yellow solid is suspended in 500 ml. of commercial absolute ethanol in a 1-l., three-necked, round-bottomed flask fitted with a rubber-tube sealed mechanical glass stirrer, a reflux condenser (Note 1), and a thermometer reaching to the bottom of the flask. The suspension is stirred and heated (Note 3) to 50°, and 50 g. (2.17 g. atom) of freshly cut sodium is added in quantities of about 10 g. each to the stirred mixture over a period of 5 minutes. The reaction mixture boils vigorously (Note 4), and stirring is continued for an additional 15 minutes. The

reaction mixture is then cooled and carefully diluted with 750 ml. of water. The white solid which separates is 9,10-dihydroanthracene, and it is collected on a Büchner funnel, washed with 300 ml. of water, and dried in air. It is recrystallized from ethanol (about 250–300 ml. of solvent is required), and the crystals are collected on a Büchner funnel, washed with 20 ml. of cold ethanol, and dried in air. The yield of dry 9,10-dihydroanthracene in the form of broad, colorless needles, m.p. 108–109°, is 38–40 g. (75–79%) (Note 5).

2. Notes

1. An efficient 12-in., double-surface, all-glass condenser should be used with an outlet tube carrying the evolved hydrogen into a good hood vent.

2. A purified grade of anthracene (blue fluorescence, m.p. 216°) should be used.

3. An electric heating mantle should be used. No free flames should be present anywhere near the reaction flask.

4. The reaction may be controlled by removing the heat source or slowing down the rate of stirring or both.

5. The 9,10-dihydroanthracene may be purified further by steam distillation from an aqueous suspension followed by recrystallization of the dried product from ethanol.

3. Methods of Preparation

The procedure described is adapted from the preparation outlined by Wieland.²

4. Merits of Preparation

9,10-Dihydroanthracene has been used as one of the hydrogen transfer reagents in a series of homolytic hydrogen transfer reactions by Braude, Jackman, and Linstead³ and as a hydrogen donor for the hydrogenation of thiyl radicals to form thiols.⁴

¹ Applied Chemistry Department, Northampton College of Advanced Technology, London, England.

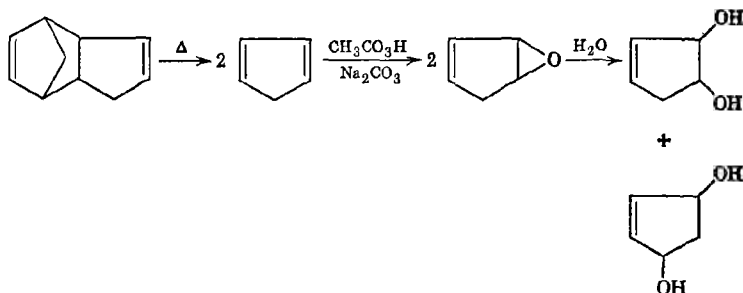
² H. Wieland, *Ber.* **45**, 492 (1912).

³ E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, **1954**, 3548.

⁴ A. F. Bickel and E. B. Kooymann, *Nature*, **170**, 211 (1952).

DIHYDROXYCYCLOPENTENE

(Cyclopentenediol)

Submitted by M. KORACH, D. R. NIELSEN, and W. H. RIDEOUT.¹

Checked by WILLIAM G. DAUBEN and CLIFTON ASHCRAFT.

1. Procedure

In a 1-l. three-necked flask equipped with a dropping funnel, a thermometer, and an efficient fractionation column fitted with either a vapor- or liquid-splitting head (Note 1) is placed 400 ml. of mineral oil. The oil is heated to 240–270° and dicyclopentadiene (Note 2) is added at the rate of 5–10 ml. per minute. The reflux ratio and the rate of addition of dicyclopentadiene are adjusted to maintain the distillation head temperature at 40°. The cyclopentadiene is collected in a Dry Ice-acetone receiver (Note 3).

In a 1-l. three-necked flask fitted with a scaled stirrer, a thermometer, and a connecting tube with parallel side arm to which is attached an addition funnel and a reflux condenser are placed 56 g. (0.81 mole) of 96% cyclopentadiene, 106 g. (1.0 mole) of anhydrous sodium carbonate, and 500 ml. of methylene chloride. A solution of 2 g. of sodium acetate in 76 g. of 40% peracetic acid (0.40 mole) (Note 4) is added, with stirring, over a period of 30–45 minutes, and the temperature is maintained at 20° by intermit-

tent external cooling. The resulting mixture is stirred for an additional hour at room temperature (Note 5). The solid in the reaction is removed by suction filtration, and the filter cake is washed three times with 75 ml. of methylene chloride. The combined filtrate and washings are added, with rapid stirring, over a period of 1 hour, to 250 ml. of cold distilled water (maintained at 5–10° by external cooling) contained in a 2-l. three-necked flask fitted with a condenser, a sealed stirrer, and an addition funnel (Note 6). The stirring is continued for 1 hour as the temperature is allowed to rise to room temperature, the layers are separated, and the lower methylene chloride layer is extracted twice with 25 ml. of distilled water. The aqueous extracts are combined with the aqueous phase obtained from the hydrolysis reaction, and the combined solution is distilled at approximately 30 mm. pressure to remove the water (Note 7). The residue is distilled at reduced pressure to give 26–28 g. of colorless oil, b.p. 82–105°/1 mm. (Note 8). The yield of mixed cyclopentenediols is 65–70% based on the quantity of peracetic acid used.

The mixed cyclopentenediols can be separated by distillation through a 60-cm. spinning band column. The yield of pure 3-cyclopentene-1,2-diol, b.p. 65–68°/1 mm., n_D^{20} 1.4941–1.4951, is 4.5–5.5 g., and the yield of pure 2-cyclopentene-1,4-diol, b.p. 92–95°/1 mm., n_D^{20} 1.5000–1.5010, is 17–20 g. (Note 9).

2. Notes

1. The checkers used a 1 x 24 in. column packed with glass helices.

2. Commercially available dicyclopentadiene of 95% or 70% purity may be used. The higher-purity material yields a less colored product.

3. Any ice present in the product can be removed by filtration of the cyclopentadiene through glass wool. Cyclopentadiene can be stored at Dry Ice temperatures in a tightly capped bottle for several weeks without serious loss due to dimerization. Purification of a stored sample can be effected by distillation through a short Vigreux column at 10–30 mm. pressure and collection of the product in a receiver cooled by a Dry Ice-acetone bath until

the temperature in the distilling flask rises to 10°. The distillate contains approximately the same concentration of cyclopentadiene as the freshly purified material (95–96%).

4. Peracetic acid (40%) is available commercially. Since the epoxycyclopentene reacts rapidly with water, it is desirable to keep the water content of the peracetic acid solution as low as possible. This is the reason for the use of the concentrated peracetic acid solution.

The peracetic acid content of the reagent may be determined by adding an aliquot to an equal volume of ice and water and titrating first with ceric sulfate solution until the orange color of the ceric ion remains (to eliminate hydrogen peroxide) and then adding potassium iodide and titrating with standard sodium thiosulfate solution.

5. The extent of peracetic acid consumption can be determined by titration of an aliquot as described in Note 4.

6. Distilled epoxycyclopentene can be hydrolyzed under identical conditions. However, distillation of the crude epoxide has occasionally resulted in a rapid, highly exothermic reaction when the pot temperature rises above 60°. The safest method for isolating the epoxide from the crude product is to remove the methylene chloride by distillation at atmospheric pressure until the pot temperature reaches 50°, then strip off crude epoxycyclopentene at reduced pressure and at a temperature below 50°. The apparatus should be shielded and the temperature in the distillation flask should be monitored. The crude distillate of epoxide and methylene chloride can be safely redistilled at 75–100 mm. pressure.

7. A rotatory evaporator has been found to be quite suitable for the rapid removal of water.

8. In some cases the distillate is yellow. The color can be removed by redistillation in the presence of 0.1% anhydrous sodium carbonate.

9. The purity of the distillation fractions can be determined by gas-liquid chromatography, using a 5 ft. x ¼ in. column containing 20% Carbowax at a temperature of 200°.

3. Methods of Preparation

Cyclopentenediol isomers have previously been prepared by hydrolysis of acetates produced by reaction of dibromocyclopentene with potassium acetate in acetic acid;² by reaction of cyclopentene with selenium dioxide in acetic anhydride;³ or by reaction of cyclopentadiene with phenyl iodosoacetate,⁴ with lead tetraacetate,⁵ or with peracetic acid in the absence of base.⁶ Preparation of cyclopentenediol without intermediate formation of acetates has been accomplished by reaction of cyclopentadiene with hydrogen peroxide in the presence of osmium tetroxide in *tert*-butanol,⁷ and by reaction of cyclopentadiene with peracetic acid in a methylene chloride suspension of anhydrous sodium carbonate, followed by hydrolysis of the resulting epoxycyclopentene.⁸

4. Merits of Preparation

The present method of preparation utilizes inexpensive, readily available, non-toxic reagents, is less laborious than previous methods, produces an easily purified product, and results in improved yields (65–70% vs. 10–50% for the older methods). It is a useful starting material for a variety of compounds as illustrated by the preparations of 2-cyclopentenone (p. 38) and 2-cyclopentene-1,4-dione (p. 36).

¹ Columbia-Southern Chemical Corp., subsidiary of Pittsburgh Plate Glass Co., P. O. Box 4026, Corpus Christi, Texas.

² A. T. Blomquist and W. G. Mayes, *J. Org. Chem.*, **10**, 134 (1945).

³ E. Dane, J. Schmitt, and C. Rautenstrauch, *Ann.*, **532**, 29 (1937).

⁴ R. Criegee and H. Beucker, *Ann.*, **541**, 218 (1939).

⁵ W. G. Young, H. K. Hall, Jr., and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4338 (1956).

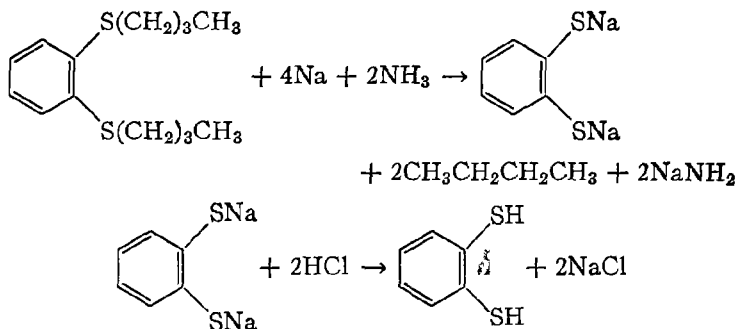
⁶ L. N. Owen and P. N. Smith, *J. Chem. Soc.*, **1952**, 4035.

⁷ N. A. Milas and L. S. Maloney, *J. Am. Chem. Soc.*, **62**, 1841 (1940).

⁸ M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Am. Chem. Soc.*, **82**, 4328 (1960).

1,2-DIMERCAPTOBENZENE

(o-Benzenedithiol)

Submitted by ALDO FERRETTI.¹Checked by WILLIAM E. PARHAM, WAYLAND E. NOLAND, and
JAMES R. THROCKMORTON.

1. Procedure

A 200-ml. two-necked flask is fitted with an efficient Dry Ice-isopropyl alcohol condenser connected to a soda-lime tube, a magnetic stirrer, and a gas inlet tube. Isopropyl alcohol and Dry Ice are added to the condenser while the flask and condenser are flushed with dry nitrogen. The flask is immersed in a Dry Ice-isopropyl alcohol bath, and a vigorous stream of dry ammonia is introduced into the system. When about 80 ml. of liquid ammonia is condensed, the gas inlet tube is replaced with a ground-glass stopper. The cooling bath is removed, stirring is started, and 5.1 g. (0.020 mole) of 1,2-bis(*n*-butylthio)benzene (Note 1) is quickly introduced (Note 2).

Sodium is now added in small pieces; the solution is allowed to decolorize before each successive piece is added. A water bath

is placed occasionally under the flask to ensure continuous ebullition of ammonia. The blue color will persist for at least 15 minutes after 1.6 g. (0.070 g. atom) of sodium has been added. The excess sodium is then destroyed by *cautious* addition of 6 g. (0.11 mole) of ammonium chloride, with stirring. Cooling and stirring are stopped, and a slow stream of argon is passed in for a period of about 12–15 hours. The white solid residue is transferred to a beaker, and 300 g. of ice water is added, together with sufficient pellets of sodium hydroxide to make the solution alkaline. The alkaline solution is then extracted twice with ether and the ether extracts discarded. The solution is then acidified to Congo red with cold 1:1 (by volume) hydrochloric acid and extracted three times with ether. The ether extracts are combined, washed with water, and dried over anhydrous sodium sulfate. The ether is evaporated and the 1,2-dimercaptobenzene is distilled under reduced pressure under an atmosphere of nitrogen, giving a product which boils at 95°/5 mm. and usually solidifies after distillation (Note 3). The yield is 1.6–2.4 g. (56–85%) (Note 4).

2. Notes

1. The preparation of 1,2-bis(*n*-butylthio)benzene is described elsewhere in this volume.²

2. 1,2-Bis(*n*-butylthio)benzene is only slightly soluble in liquid ammonia. Stirring must be very efficient during the addition and subsequently during the reaction to prevent the drops of 1,2-bis(*n*-butylthio)benzene from collecting as a solid mass. If this happens, the time necessary for completion of the reaction, and the quantity of sodium necessary for dealkylation, must be increased. The checkers found that the 1,2-bis(*n*-butylthio)benzene invariably collected as several solid masses and that it was always necessary to add additional sodium, about 0.9 g.

3. The reported melting point is 27–28°.³

4. The reported yield is 2.0 g. (70%) of an oil, b.p. 102°/6.5 mm.³ A similar procedure has been used by the submitter to prepare 1,4-dimercaptobenzene, 2,5-dimercaptotoluene, 1,3,5-trimercaptobenzene, 2,4,6-trimercaptomesitylene, and 4,4'-dimercaptobiphenyl.⁴

3. Methods of Preparation

The present procedure is that of Adams and Ferretti.³ Another method is the reduction of 1,2-benzenedisulfonyl chloride with zinc powder.⁴ In a third method ⁵ a 2-aminomercaptobenzene is diazotized and converted to an intermediate xanthate and then to the corresponding mercaptosulfonic acid. The latter can be converted to the dimercaptan either by: (1) oxidation to a disulfonic acid, conversion to the disulfonyl chloride, and reduction to the dimercaptan, or (2) mild oxidation to the corresponding disulfide, conversion to the sulfonyl chloride disulfide, and reduction to the dimercaptan.

4. Merits of the Preparation

The present procedure, when combined with the accompanying preparation of aryl sulfides (p. 22), provides a convenient and general method for preparing aryl mercaptans from aromatic halides.

¹ Via Martiri Triestini, 12, Milan, Italy.

² R. Adams, W. Reifschneider, and A. Ferretti, this volume, p. 22.

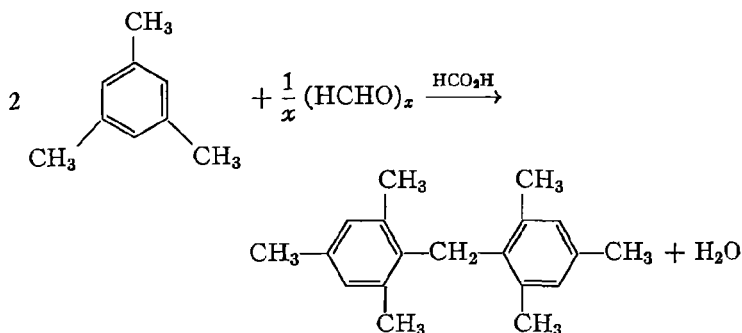
³ R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4939 (1959).

⁴ W. R. H. Hurlley and S. Smies, *J. Chem. Soc.*, 1926, 1821.

⁵ P. C. Guha and M. N. Chakladar, *J. Indian Chem. Soc.*, **2**, 318 (1925).

DIMESITYLMETHANE

(Methane, dimesityl-)

Submitted by JOHN H. CORNELL, JR., and MORTON H. GOLLIS.¹

Checked by WILLIAM E. PARHAM and JAMES TOGEAS.

1. Procedure

Into a 5-l. round-bottomed flask fitted with stirrer, thermometer, and reflux condenser are introduced 165 g. (5 moles) of 91% paraformaldehyde (Note 1) and 1250 g. (24 moles) of 88% formic acid (Note 2). The mixture is heated to 80° with stirring and is stirred until the paraformaldehyde has dissolved. To the stirred mixture is rapidly added 1.8 kg. (15 moles) of mesitylene and the whole heated under reflux for 6 hours (Note 3).

On cooling to room temperature, a large mass of dirty-yellow crystals separates. The liquid layers are decanted from the yellow solid, and the aqueous (lower) layer is separated and discarded. The solid is washed in the reaction flask by stirring with 500 ml. of benzene. This slurry of solid in benzene is filtered and the solid sucked dry on a Büchner funnel. This filtrate is combined with the upper organic layer from the original reaction mixture, and the combined benzene solution is washed with 500 ml. of

water, 500 ml. of 2–3% aqueous sodium carbonate (Note 4), and 200 ml. of saturated sodium chloride solution. Benzene and water are removed from this solution by distillation at atmospheric pressure. The still residue is cooled to room temperature, and precipitated solid is removed by filtration and added to the large crop of solid from the original reaction mixture. The combined solids are washed twice with 300 ml. of water, once with 400 ml. of 2–3% aqueous sodium carbonate, and once with 300–400 ml. of water and sucked dry on a Büchner funnel.

The yield is 779 g. of crude dimesitylmethane (62% of theoretical) melting at 128.5–131°, uncor.; its purity as determined by vapor-phase chromatography is 99.9 mole per cent (Note 5).

2. Notes

1. The checkers used 150 g. (5 moles) of paraformaldehyde obtained from Eastman Organic Chemicals.

2. Contact with formic acid and inhalation of its vapors should be avoided.

3. When a smaller ratio of mesitylene to formaldehyde was used, a considerable amount of polymeric residue was formed and the yield was very much reduced.

4. It is advisable to add the sodium carbonate solution cautiously and with good agitation to avoid a violent evolution of carbon dioxide.

5. The crude product is pure enough for most purposes. However, for catalytic reduction to bis(2,4,6-trimethylcyclohexyl)-methane, the residual acid must be removed by dissolving the solid in hot benzene and stirring or shaking with dilute aqueous sodium carbonate solution until the washings are basic; this is followed by a water wash and drying.

The solid can be recrystallized from boiling benzene and precipitated with about 0.15 part of boiling methanol to give white platelets (68%), m.p. 133–135°, plus a second, less pure crop (22%) melting at 128–133°. Reported for dimesitylmethane,² m.p. 134.4–135.4°, b.p. 212–213°/21 mm.

The reaction has been scaled up tenfold using a 50-l. flask without changes in procedure and in the same yield.

3. Methods and Merits of Preparation

Substituted diarylmethanes have been prepared from formaldehyde and a variety of its derivatives. Sulfuric acid is a common catalyst.^{1,2} The procedure described is based on the general method of Gordon, May, and Lee.⁴ Formic acid is preferable to sulfuric acid as a catalyst because it is capable of acting as a solvent as well, thus eliminating troublesome emulsions. Side reactions such as sulfonation are avoided.

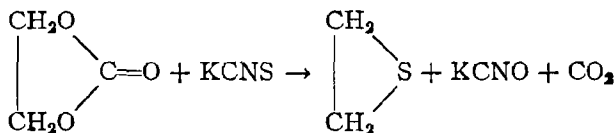
¹ Monsanto Chemical Company, Special Projects Department, Boston 49, Mass.

² C. M. Welch and H. A. Smith, *J. Am. Chem. Soc.*, **73**, 4391 (1951).

³ I. G. Matveev, D. A. Drapkina, and R. L. Globus, *Trudy Vsesoyuz. Nauch.-Issledovatel. Inst. Khim. Reaktivov*, **1956**, No. 21, 83 [*C.A.*, **52**, 15474 (1958)].

⁴ L. B. Gordon, P. D. May, and R. J. Lee, *Ind. Eng. Chem.*, **51**, 1275 (1959).

ETHYLENE SULFIDE



Submitted by SCOTT SEARLES, EUGENE F. LUTZ, HIGH R. HAYS, and HARLEY E. MORTENSEN.¹

Checked by MELVIN S. NEWMAN and BERNARD C. REAM.

1. Procedure

Into a 250-ml., two-necked, round-bottomed flask equipped with a thermometer (Note 1) and leading to a condenser equipped with a distillation head and a receiver is placed 145 g. (1.5 mole) of potassium thiocyanate (Note 2). The system is evacuated to about 1 mm., and the flask is heated with a free flame until the temperature of the molten salt is in the 165–175° range (Note 3). After the flask has been heated for 15 minutes, it is cooled to room temperature and 88 g. (1.0 mole) of ethylene carbonate

(Note 4) is added. The apparatus is reconnected and the receiver protected with a calcium chloride tube.

The reaction flask is slowly heated by means of a sand bath, and the receiver is cooled in a Dry Ice-acetone bath. When the temperature in the fused potassium thiocyanate layer reaches 95°, reaction occurs. Ethylene sulfide distils and is collected in the receiver. Heating is continued for about 3 hours at 95–99° (Note 5). The distillate amounts to 41–45 g. (68–75%) (Note 6) and is sufficiently pure to be used directly (Note 7).

2. Notes

1. The thermometer may be inserted through a neoprene stopper in one neck or into a suitably designed thermometer well.

2. J. T. Baker's analytical grade was used.

3. The purpose of this operation is to ensure dryness, as potassium thiocyanate is hygroscopic. The presence of even small amounts of water is detrimental to the yield. The initially colorless salt melts to a blue liquid. On cooling, this solidifies to a colorless solid.

4. Ethylene carbonate obtained from the Eastman Kodak Company or the Jefferson Chemical Company was vacuum distilled and the fraction, b.p. 125°/10 mm., was used.

5. Differences in the rate of heating and time of heating cause small changes in the yield of ethylene sulfide obtained. If the time of heating is reduced and the rate of heating increased, the yield drops somewhat. For many purposes the saving in time offsets the higher yield obtained under optimum conditions. The submitters have obtained yields in the 81–87% range.

6. This product can be stored at room temperature for several weeks without polymerization. On distillation, pure ethylene sulfide, b.p. 54.0–54.5°, n_D^{20} 1.4960, is obtained.

7. For example, this product is suitable for reaction with amines.²

3. Methods of Preparation

Ethylene sulfide has been prepared by the reaction of ethylene oxide with aqueous potassium thiocyanate;^{2,3} by the reaction of

2-chloroethyl mercaptan with aqueous sodium bicarbonate;⁴ by the reactions of 2-chloroethylthiocyanate⁵ and 1,2-dithiocyanethane⁶ with alcoholic sodium sulfide; and by the thermal decomposition of monothiolethylene carbonate.⁷

4. Merits of Preparation

The advantage of the present procedure is the easy availability at low expense of the starting material, ethylene carbonate.⁸ Its advantages over the other methods are high yields and degree of purity of the product, combined with greater simplicity of procedure.

¹ Department of Chemistry, Kansas State University, Manhattan, Kansas.

² H. R. Snyder, J. M. Steward, and J. B. Ziegler, *J. Am. Chem. Soc.*, **69**, 2672 (1947).

³ G. I. Braz, *Zhur. Obshchei Khim.*, **21**, 688 (1951) [*C. A.*, **45**, 9453 (1951)].

⁴ W. Coltof, U. S. pat. 2,183,860 (1940) [*C. A.*, **34**, 2395 (1940)]. Also N. V. de Bataafsche Pet. Maatschappij, Brit. pat. 508,932 (1939); Dutch pat. 47,835 (1940).

⁵ M. M. Delepine, *Bull. soc. chim. France*, **27**, 740 (1920).

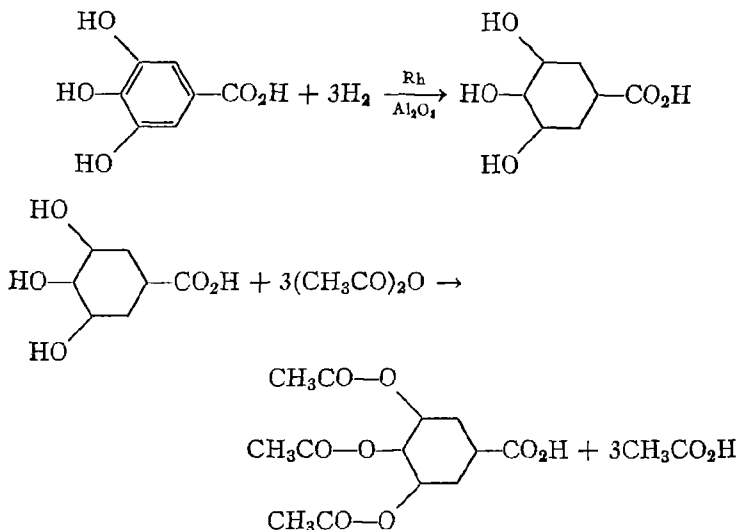
⁶ M. M. Delepine and S. Eshenbrenner, *Bull. soc. chim. France*, **33**, 703 (1923).

⁷ D. D. Reynolds, *J. Am. Chem. Soc.*, **79**, 4951 (1957).

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HEXAHYDROGALLIC ACID AND HEXAHYDROGALLIC ACID TRIACETATE

(Cyclohexanecarboxylic acid, 3,4,5-triol and triacetate)



Submitted by ALBERT W. BURGSTAHLER and ZOE J. BITHOS.¹
Checked by R. P. LUTZ and JOHN D. ROBERTS.

1. Procedure

A. Hexahydrogallic acid. A solution of 50 g. (0.266 mole) of recrystallized gallic acid monohydrate (Note 1) in 225 ml. of 95% ethanol (Note 2) is placed in a 1-l. high-pressure hydrogenation bomb (Note 3) with 8 g. of 5% rhodium-alumina catalyst (Note 4). The bomb is then closed, hydrogen admitted at full tank pressure (2200 lb., Note 5), and the temperature raised to 90–100° (Note 6) while agitation is commenced. When the hydrogen uptake is complete (8–12 hours), heating is discontinued and the bomb is allowed to cool. The residual hydrogen is bled off,

and the contents of the bomb are rinsed out with two 40-ml. portions of warm distilled water and then heated to boiling on the steam bath for 5 minutes to dissolve any product which has crystallized on the catalyst. After removal of the catalyst by suction filtration (Note 7), the colorless filtrate (Note 8) is concentrated on the steam bath under reduced pressure (preferably using a rotary evaporator). The viscous residue which may have begun to deposit crystals is diluted with 75–100 ml. of ethyl acetate and the product allowed to crystallize at 0° for several hours or overnight. The product is collected on a 9-cm. Büchner funnel and washed with 75 ml. of cold 3:1 ethyl acetate-absolute ethanol and finally with 100 ml. of 30–40° petroleum ether. When dry, it weighs 21–24 g. (45–51%); an additional 2–4 g. can usually be obtained by concentration of the mother liquors and crystallization from ethyl acetate. Recrystallization is achieved by dissolution of the combined products in the minimum amount of boiling water (Note 9), suction filtration if necessary to remove suspended matter (Note 10), addition of hot ethanol to bring the volume of the solution to about 110 ml., and finally addition of about 35 ml. of acetone, sufficient to produce a faint cloudiness. The solution is allowed to cool slowly to room temperature and is then stored at 0° overnight. The fine, colorless crystals are collected on a 7-cm. Büchner funnel and washed with 80 ml. of cold 5:3 absolute ethanol-acetone, then with 100 ml. of 30–40° petroleum ether. The product when dry weighs 18–20 g. (38–43%). The yield may be increased somewhat by concentration of the combined mother liquor and washings, and treatment as before with ethanol and acetone. The melting point is not a useful criterion of purity, since the hexahydrogallic acid decomposes on heating (Note 11). The product is apparently substantially the all-*cis* isomer.²

B. *Hexahydrogallic acid triacetate*. A suspension of 10 g. (0.057 mole) of the dry, recrystallized hexahydrogallic acid in 40 ml. of acetic anhydride is treated with 1 drop of concentrated sulfuric acid, which initiates the reaction (Note 12). Most of the solid then goes into solution with some evolution of heat. The reaction is completed on a steam bath for 30 minutes. The acetic acid and most of the excess anhydride are then removed

on the steam bath under reduced pressure with the aid of an oil pump. Twenty-five milliliters of water is added, and the mixture is shaken and heated on the steam bath for 10 minutes in order to hydrolyze residual acetic anhydride and the mixed anhydride of the product and acetic acid. Most of the solvent is then removed under reduced pressure on the steam bath; the product usually crystallizes during this process. About 15 ml. of water is added, and the mixture is heated on the steam bath until the solids dissolve. The solution is first allowed to cool slowly to room temperature and then stored at 0° for several hours to complete crystallization. The colorless crystals are collected, washed rapidly with 10–15 ml. of cold water, and dried at 60° or in a vacuum desiccator at room temperature. The yield is 15–17 g., m.p. 152–154°. The product may be recrystallized by dissolution in 25–30 ml. of hot acetone and addition of 50 ml. of 30–40° petroleum ether. The colorless crystalline granules are collected by suction filtration and washed with a small amount of 2:1 petroleum ether(30–40°)-acetone. The recrystallized product when dried amounts to 13.5–14.5 g. (78–84%), m.p. 155–156° (Note 13).

2. Notes

1. Gallic acid is conveniently recrystallized from water (heated to boiling, then cooled to 0°) with treatment with decolorizing carbon if necessary.

2. Absolute alcohol leads to partial esterification of the product; a higher percentage of water deactivates the catalyst.

3. A glass liner may be helpful in preventing poisoning of the catalyst. Stainless-steel vessels usually require one run to "condition" the surfaces before the reported yields can be obtained.

4. The catalyst is available from Englehardt Industries, Inc., Chemical Division, Newark, New Jersey. The activity appears to vary slightly with different lots. Other catalysts, such as palladium, platinum, and ruthenium on various supports, or Raney nickel, were found to be much less satisfactory or completely ineffective.

5. Pressures lower than 1800 lb. usually lead to incomplete reduction.

6. Reduction is inconveniently slow at lower temperatures; temperatures higher than 125° tend to favor esterification and other by-product formation.

7. The recovered catalyst (along with fresh catalyst) can be reused several times for further reductions.

8. The ferric chloride test is negative, and the filtrate remains colorless when hydrogenation is complete. A deep blue color (due to the presence of gallic acid or dihydro products) appears when it is not, but the hexahydro acid can usually be isolated in good yield in spite of this.

9. A hot plate equipped with a magnetic stirrer is especially convenient for this operation.

10. Any excess water used to transfer the solution or to wash the filter must be evaporated; otherwise the recovery is smaller.

11. Decomposition usually begins at about 190°, with melting at 198–200°. Melting points as high as 203–204° have been observed by the submitters and checkers. The purity of successively recrystallized products may be compared by immersing the samples enclosed in capillary tubes of uniform dimensions in a melting-point bath maintained at a constant temperature of 200° and noting the times required for complete melting.

12. Acetylation in pyridine is comparatively less satisfactory and considerably more inconvenient.

13. Using a Kofler melting-point block fitted with a microscope, the checkers observed a crystal transition at about 140° with final, moderately sharp, melting at 157–158°.

3. Methods of Preparation

The all-*cis* diastereoisomer of hexahydrogallic acid has been prepared from gallic acid in 13–19% over-all yield by a two-stage reduction, first with Raney nickel in basic solution to form the somewhat difficultly isolated dihydro intermediate, and then with a platinum catalyst to complete the reduction.¹ The present procedure is based on a published preparation.²

The acetylation procedure described here is based on that which has already been published.³

4. Merits of Preparation

The direct reduction of gallic acid described here illustrates the virtue of the rhodium-on-alumina catalyst to achieve the perhydrogenation of polyhydroxylated aromatic compounds with minimal attendant hydrogenolysis. A closely related hydrogenation, that of pyrogallol, to yield a dihydro intermediate,³ and also the direct reduction of pyrogallol with palladium-on-strontium carbonate to afford the all *cis*-pyrogallitol (1,2,3-cyclohexanetriol) have been reported.⁴

¹ Department of Chemistry, University of Kansas, Lawrence, Kansas.

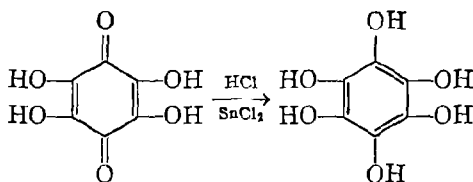
² A. W. Burgstahler and Z. J. Bithos, *J. Am. Chem. Soc.*, **82**, 5466 (1960).

³ W. Mayer, R. Bachmann, and F. Kraus, *Ber.*, **88**, 316 (1955).

⁴ W. R. Christian, C. J. Gogek, and C. B. Purves, *Can. J. Chem.*, **29**, 911 (1951); cf. S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, **1957**, 3682.

HEXAHYDROXYBENZENE

(Benzenehexol)



Submitted by A. J. FATIADI and W. F. SAGER.¹

Checked by B. C. McKUSICK and J. K. WILLIAMS.

1. Procedure

One hundred grams (0.44 mole) of stannous chloride dihydrate is added to a boiling solution of 10 g. (0.058 mole) of tetrahydroxyquinone¹ in 200 ml. of 2.4*N* hydrochloric acid contained in a 1.5-l. beaker. The initial deep-red color disappears, and grayish crystals of hexahydroxybenzene precipitate. Two hundred fifty milliliters of 12*N* hydrochloric acid is added, and the mixture is heated

to boiling with constant stirring. The beaker is removed from the hot plate, an additional 600 ml. of 12*N* hydrochloric acid is added, and the solution is cooled in a refrigerator. The hexahydroxybenzene is collected on a Büchner funnel fitted with a sintered-glass disk (Note 1) and sucked dry.

The crude hexahydroxybenzene is dissolved in 450 ml. of hot 2.4*N* hydrochloric acid containing 3 g. of hydrated stannous chloride and 1 g. of decolorizing carbon. The solution is filtered while hot, and the carbon is rinsed with 75 ml. of boiling water that is combined with the filtrate. One liter of 12*N* hydrochloric acid is added, and the mixture is cooled in a refrigerator. The snow-white crystals of hexahydroxybenzene that separate are collected under carbon dioxide or nitrogen (Note 2) on a Büchner funnel fitted with a sintered-glass disk. The hexahydroxybenzene is washed with 100 ml. of a cold 1:1 mixture of ethanol and 12*N* hydrochloric acid and dried in a vacuum desiccator over sodium hydroxide pellets; yield 7.1–7.8 g. (70–77%). It fails to melt on a hot plate at 310° (Note 3).

2. Notes

1. Filter paper cannot be used because it is attacked by strong hydrochloric acid.

2. By rapid manipulation it is possible to obtain a product of fair quality. The moist product is susceptible to air oxidation, as is shown by a development of pink coloration on the crystals. The filtration is best carried out under a blanket of carbon dioxide or nitrogen obtained by inverting a funnel attached to a source of carbon dioxide or nitrogen over the Büchner funnel.

3. The decomposition point of hexahydroxybenzene is not a good criterion of purity. If the product is light in color, there can be no significant amount of oxidized material in it, for even traces of tetrahydroxyquinone cause intense coloration. Decomposition of a sample with nitric acid followed by evaporation and ignition of the residue should give a negligible amount of tin oxide. The product can be characterized as the hexaacetate, m.p. 202–203°, by treating it with acetic anhydride and sodium acetate.³

3. Methods of Preparation

The present procedure is a modification of the procedure of Anderson and Wallis.⁴ Hexahydroxybenzene can also be prepared by acidic hydrolysis of potassium carbonyl³ or by nitration and oxidation of diacetyl hydroquinone.⁵

4. Merits of the Procedure

This is the most convenient synthesis of hexahydroxybenzene, and the present procedure gives better yields than reported by Anderson and Wallis.⁴ Hexahydroxybenzene is of interest as the most highly hydroxylated member of the polyhydroxybenzene family.

It has been used as a source of the biologically important *myo*-inositol^{6,7} (1235/46 isomer) by hydrogenation over palladium and of *cis*-inositol (123456 isomer) by hydrogenation over palladium-on-carbon.

¹ Department of Chemistry, The George Washington University, Washington 6, D. C.

² A. J. Fatiadi and W. F. Sager, this volume, p. 90.

³ B. Nietzki and T. Benckiser, *Ber.*, **18**, 1834 (1885).

⁴ R. C. Anderson and E. S. Wallis, *J. Am. Chem. Soc.*, **70**, 2931 (1948).

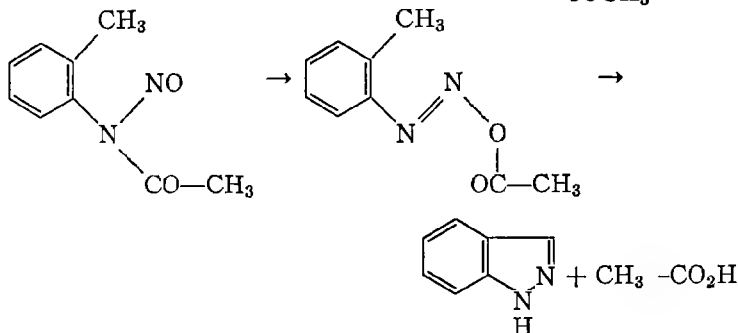
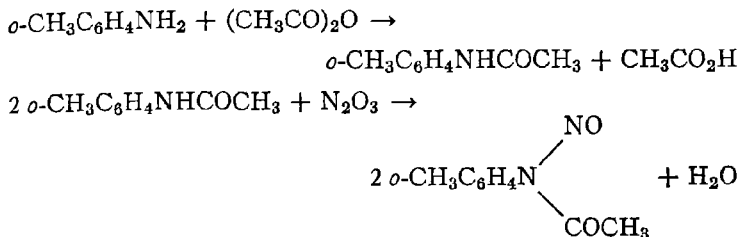
⁵ B. Nietzki and T. Benckiser, *Ber.*, **18**, 500, 1842 (1885).

⁶ H. Wieland and R. S. Wishart, *Ber.*, **47**, 2082 (1914).

⁷ S. J. Angyal and D. J. McHugh, *Chem. & Ind. (London)*, **1955**, 947.

INDAZOLE

(Benzopyrazole)



Submitted by ROLF HUISGEN and KLAUS BAST.¹

Checked by W. E. PARHAM, WAYLAND E. NOLAN, and
JOHN W. DRENCKPOHL.

1. Procedure

Ninety grams (90.2 ml., 0.839 mole) of *o*-toluidine is slowly added to a mixture of 90 ml. of glacial acetic acid and 180 ml. (1.90 mole) of acetic anhydride contained in a 750-ml. two-necked flask equipped with a thermometer and a two-hole cork stopper for a gas inlet tube (Note 1). Acetylation occurs with evolution of heat. The mixture is cooled in an ice bath (Note 2) and nitrosated by rapid admission of a stream of nitrous gases (Note 3). The nitrous gases are obtained by the action of nitric

acid (density 1.47) on sodium nitrite (Note 4). Technical grade, large-grain sodium nitrite (180 g.) is placed in a 1-l. suction flask to which a dropping funnel is fitted by means of a rubber stopper (Note 5). The acid (a total of about 250 ml. is used) is added dropwise from the dropping funnel. The rate of the gas evolution should be such that the temperature of the reaction mixture is kept between $+1^{\circ}$ and $+4^{\circ}$ (Note 6). The gas is passed through a wash bottle (with inlet and outlet positions reversed) containing some glass wool and positioned between the generating flask and the reaction flask. After about 6 hours the nitrosation is complete, and the solution exhibits a permanent black-green color due to excess N_2O_3 (Note 7).

The solution of N-nitroso-*o*-acetotoluidide is poured onto a mixture of 400 g. of ice and 200 ml. of ice water in a beaker, covered loosely with a watch glass, and allowed to stand in an ice bath for 2 hours. The oil which separates is transferred to a separatory funnel and extracted by shaking with several portions of benzene (total volume 500 ml.). The combined extract is washed with three 100-ml. portions of ice water and, after shaking with 30 ml. of methanol to remove remaining acetic anhydride, is allowed to stand, lightly covered, in an ice bath for 1 hour. Next, the mixture is washed with three 100-ml. portions of ice water, and the cold benzene solution is allowed to stand, loosely covered, over calcium chloride in the refrigerator overnight (Note 8). The brown solution is decanted from the drying agent into a 3-l. Erlenmeyer flask, and the calcium chloride is washed (by decantation) with 800 ml. of benzene. The combined benzene layer and washings are warmed to 35° in a large water bath and maintained at this temperature for 1 hour (internal temperature, Notes 9 and 10), and then at $40-45^{\circ}$ for 7 hours. These temperatures must be strictly adhered to; otherwise overheating can occur (Note 11).

After the completion of the decomposition, the solution is boiled for a short time by heating on a steam bath. The cooled solution is transferred to a separatory funnel and extracted with 200 ml. of 2*N* hydrochloric acid and then with three 50-ml. portions of 5*N* hydrochloric acid. The combined acid extracts are treated with excess ammonia, at which point the indazole pre-

cipitates. The mixture is kept in the refrigerator for 2 hours, and the solid is then collected on a Büchner funnel, washed with water, placed in a beaker covered with a piece of paper, and dried overnight at 100–105°. The yield of crude, light brown indazole, m.p. 144–147°, is 36–46 g. (36–47%) (Note 12). For purification, vacuum distillation in a Claisen flask, modified for distillation of solids, is suitable. This gives 33–43 g. of colorless indazole (b.p. 167–176°/40–50 mm.) with a melting point of 148° (Note 13).

2. Notes

1. The inlet tube should not be too narrow and should dip far enough into the reaction mixture to permit agitation of the reaction mixture by the gas stream.

2. Crystallization of *o*-acetotoluidide sometimes occurs at this stage and is allowed to go to completion. This is indicated by a decrease in the evolution of heat of crystallization. Addition of nitrous acid is not begun until the reaction mixture has reached 3°.

3. No harm is done by the separation of *o*-acetotoluidide, which sometimes occurs at this point.

4. The acid (density 1.47) is obtained by diluting 200 ml. of fuming nitric acid with 70 ml. of concentrated nitric acid.

The amount of N_2O_3 in the nitrous gases depends on the density of the nitric acid used.

Density 1.40 corresponds to 13 vol. % N_2O_3 or its equivalent.

Density 1.43 corresponds to 23 vol. % N_2O_3 or its equivalent.

Density 1.45 corresponds to 41 vol. % N_2O_3 or its equivalent.

Density 1.47 corresponds to 78 vol. % N_2O_3 or its equivalent.

5. The stopper is covered with a thin layer of paraffin. At the rubber tubing connections, the ends of the glass tubes should be in contact.

6. This is accomplished with an ice bath (without added salt).

7. Should the gas evolution become sluggish after 3–4 hours, the generator may be replaced by a new one containing one-half as much sodium nitrite.

8. It is necessary to begin the preparation early in the morning in order to bring it to this stage in one day.

9. If the water bath is heated by a hot plate controlled by a thermoregulator, it is only necessary to set the temperature at the thermoregulator.

10. At the beginning, the internal temperature is about 5–10° higher than the bath temperature because of the exothermic character of the indazole formation.

11. The use of a large bath simplifies dissipation of the heat of reaction.

12. The submitters regularly obtained yields as high as 55–61% of crude indazole and 52–58% of pure indazole.

13. This pressure range is used in order to give a boiling point sufficiently above the melting point of the indazole.

3. Methods and Merits of Preparation

The preceding method is that of Huisgen and Nakaten² and is based on the preparation of indazole (ca. 40% yield) from N-nitroso-*o*-benzotoluidide discovered by Jacobson and Huber.³ Mechanistic studies² showed this reaction to be an intramolecular azo coupling with an initial acyl shift as the determining step. The yield of indazole from N-nitroso-*o*-benzotoluidide can be made almost quantitative.² Since the low solubility of *o*-benzotoluidide makes large quantities of acetic acid and acetic anhydride necessary, the method using the N-acetyl compound described here is more convenient.

With respect to time and cost, this method is superior to the five-step synthesis⁴ from anthranilic acid. Older literature sources have been cited in an earlier volume of *Organic Syntheses*.⁴ Indazole has also been prepared recently by the reaction of 2-hydroxymethylenecyclohexanone with hydrazine and dehydrogenation of the 5,6,7,8-tetrahydro derivative.⁵

¹ Institut für Organische Chemie, Universität München, München 2, Germany.

² R. Huisgen and H. Nakaten, *Ann.*, **536**, 84 (1954).

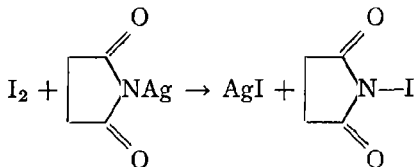
³ P. Jacobson and L. Huber, *Ber.*, **41**, 660 (1908).

⁴ E. F. M. Stephenson, *Org. Syntheses Coll. Vol. 3*, 475 (1955).

⁵ C. Ainsworth, *Org. Syntheses*, **39**, 27 (1959).

N-IODOSUCCINIMIDE

(Succinimide, N-iodo-)

Submitted by W. R. BENSON,¹ E. T. MCBEE,² and L. RAND.³

Checked by B. C. MCKUSICK and T. J. KEALY.

1. Procedure

Twenty grams (0.079 mole) of iodine and 90 ml. of dried dioxane (Note 1) are placed in a wide-mouthed, screw-cap, brown bottle of 150–200 ml. capacity. Most of the iodine dissolves. Eighteen grams (0.087 mole) of thoroughly dried N-silver succinimide (Note 2) is added, and the bottle is shaken vigorously for several minutes. The mixture is occasionally shaken in the course of an hour and then is warmed in a water bath at 50° for 5 minutes. It is now filtered hot through a Büchner funnel into a 500-ml. filter flask well wrapped with black paper or aluminum foil. The silver iodide that is collected is washed with a 10-ml. portion of warm dioxane. Carbon tetrachloride (200 ml.) is added to the combined filtrates in the filter flask, and the solution is chilled overnight at –8° to –20°. N-Iodosuccinimide separates as colorless crystals. It is collected on a Büchner funnel with as little exposure to light as possible, washed with 25 ml. of carbon tetrachloride, and dried with suction. After being dried overnight in the dark at 25°/1 mm., the N-iodosuccinimide weighs 14.3–15.1 g. (81–85% yield) and melts with decomposition at 193–199° (Note 3).

2. Notes

1. The dioxane is purified only by the use of sodium strips and distillation.³ The checkers used a newly opened bottle of "Spectroquality Reagent" dioxane (Matheson, Coleman and Bell) without further treatment.

2. N-Silver succinimide was prepared by the method of Djerassi and Lenk.⁴ The checkers rapidly added a solution of 64 g. (1.6 moles) of sodium hydroxide in 300 ml. of water dropwise to a stirred solution of 249 g. (1.47 moles) of silver nitrate in 700 ml. of water at room temperature. The silver oxide that formed was separated on a Büchner funnel and washed with water. The moist oxide was added in one portion to a boiling solution of 133 g. (1.34 moles) of succinimide in 4 l. of water. The reaction vessel was wrapped with aluminum foil in order to exclude as much light as possible. After 45 minutes, the suspension was filtered through a heated Büchner funnel into a filter flask also wrapped with aluminum foil. The filtrate was allowed to stand at room temperature overnight, during which time N-silver succinimide crystallized. The N-silver succinimide was separated on a Büchner funnel, dried in air under suction, and ground to a powder. After being dried in a vacuum oven for 1 hour at 110°, it weighed 128 g. (47%). N-Silver succinimide should be stored in a brown bottle.

3. This material is pure enough to use in the preparation of α -iodoketones. The checkers found that, after one recrystallization from a mixture of dioxane and carbon tetrachloride, the N-iodosuccinimide melted with decomposition at 195–200°. Pure N-iodosuccinimide is reported to melt at 200–201°.⁴

3. Methods of Preparation

N-Iodosuccinimide has been prepared only by the action of iodine on N-silver succinimide.^{4,5} The present procedure is essentially that of Djerassi and Lenk,⁴ with the modification that dioxane is the reaction medium instead of acetone; dioxane gives a better yield without formation of a lachrymatory by-product.

4. Merits of Preparation

N-Iodosuccinimide reacts with enol acetates derived from ketones to give α -iodoketones, and the reaction has found application in the steroid field.^{4,6} The iodination of the enol acetates seems to proceed by an ionic mechanism, and preliminary work indicates that N-iodosuccinimide is not capable of at least some of the radical-chain iodinations analogous to radical-chain brominations brought about by N-bromosuccinimide.⁴

¹ Chemistry Department, Colorado State University, Fort Collins, Colo.

² Department of Chemistry, Purdue University, Lafayette, Ind.

³ L. Fieser, *Experiments in Organic Chemistry*, 3rd ed., p. 284, D. C. Heath and Co., Boston, 1955.

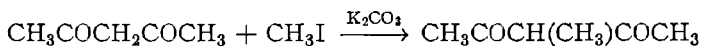
⁴ C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **75**, 3494 (1953).

⁵ N. Bunge, *Ann.*, **7** (suppl.), 117 (1870).

⁶ C. Djerassi, J. Grossman, and G. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3826 (1955).

3-METHYLPENTANE-2,4-DIONE

(2,4-Pentanedione, 3-methyl-)



Submitted by A. W. JOHNSON, E. MARKHAM, and R. PRICE.¹

Checked by VIRGIL BOEKKELHEIDE and M. KUNSTMANN.

1. Procedure

A mixture of 65.2 g. (0.65 mole) of pentane-2,4-dione, 113 g. (0.80 mole) of methyl iodide, 84 g. of anhydrous potassium carbonate (Note 1), and 125 ml. of acetone is placed in a 500-ml. round-bottomed flask fitted with a reflux condenser and a calcium chloride guard tube. The mixture is heated under reflux for 20 hours and is then allowed to cool. The insoluble material is removed by filtration and washed with acetone (Note 2). The combined filtrate and acetone washings are concentrated on the steam bath (Note 3), and the residual oil is distilled. There is

collected 56–57 g. (75–77%) of a colorless oil, b.p. 170–172°/760 mm., n_D^{24} 1.4378.

2. Notes

1. The potassium carbonate is dried at 100° for 2 hours before use.
2. Thorough washing of the inorganic residues is essential and requires about 200 ml. of acetone.
3. During removal of the acetone, potassium iodide is deposited and it is advisable to decant the crude 3-methylpentane-2,4-dione from this material before distillation.

3. Methods of Preparation

3-Methylpentane-2,4-dione has been prepared by the reaction of the sodium derivative of pentane-2,4-dione with methyl iodide in a sealed tube at 140°,² and from the sodium³ and potassium⁴ derivatives of pentane-2,4-dione and methyl iodide in alcoholic solution. It has also been prepared by the reaction of methyl iodide and pentane-2,4-dione in the presence of potassium carbonate in alcoholic or ethereal solution⁶ and in acetone solution,⁶ and by heating 2-aminopenten-4-one with methyl iodide at 100°.⁷ The present modification affords improved yields.

4. Merits of Preparation

The method presented here has also been used for the preparation of 3-ethyl- and 3-isopropylpentane-2,4-diones and is probably of general applicability in the preparation of 3-alkylpentane-2,4-diones.

¹ Department of Chemistry, University of Nottingham, Nottingham, England.

² W. R. Dunstan and T. S. Dymond, *J. Chem. Soc.*, **59**, 428 (1891).

³ J. Salkind, *Chem. Zentr.*, **1905**, II, 753.

⁴ W. H. Perkin, *J. Chem. Soc.*, **61**, 848 (1892).

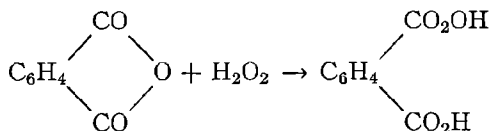
⁵ L. Claisen, *Ber.*, **27**, 3184 (1894).

⁶ K. von Auwers and H. Jacobsen, *Ann.*, **426**, 229 (1922).

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MONOPERPHTHALIC ACID

(Phthalic monoperacid)

Submitted by GEORGE B. PAYNE.¹

Checked by K. NAGARAJAN and JOHN D. ROBERTS.

1. Procedure

In a 1-l. round-bottomed flask equipped with a mechanical stirrer and cooled in an ice-salt bath is placed a solution of 62 g. (0.5 mole) of sodium carbonate monohydrate in 250 ml. of water. This is cooled to 0°, and 69 g. (63 ml., 0.6 mole) of 30% hydrogen peroxide (Note 1) is added in one portion. With the temperature at -5 to 0°, 74 g. (0.5 mole) of phthalic anhydride (Note 1) which has been pulverized to pass a 14-mesh sieve is added.

The reaction mixture is stirred vigorously at -5 to 0° for 30 minutes, then the resulting solution or suspension (Note 2) is poured into a 2-l. separatory funnel, shaken with 350 ml. of ether (Note 3), and carefully acidified with an ice-cold solution of 30 ml. of concentrated sulfuric acid in 150 ml. of water. The liberated monoperphthalic acid is extracted into the ether and removed completely from the water by extraction with two more 150-ml. portions of ether. The combined ether extracts are washed with two 200-ml. portions of 40% ammonium sulfate solution and dried overnight in a refrigerator over 50 g. of anhydrous magnesium sulfate.

The peracid content is determined by adding 30 ml. of 20% potassium iodide solution to 2 ml. of the peracid solution and, after 10 minutes, titrating the liberated iodine with 0.1 *N* thio-sulfate. The yield is 71-78 g. (78-86% based on phthalic anhydride).

If crystalline monoperphthalic acid is desired, it may be prepared as described earlier.²

2. Notes

1. Commercial phthalic anhydride and hydrogen peroxide, both of reagent grade, are used.

2. The sodium salt of monoperphthalic acid may precipitate during the reaction.

3. The ether may be used, along with a *small amount* of cold water, to effect a quantitative transfer of the suspension from reaction vessel to separatory funnel.

3. Methods of Preparation

Monoperphthalic acid has been prepared by hydrolysis of phthalyl peroxide with sodium hydroxide,³ by reaction of phthalic anhydride with excess alkaline peroxide solution,⁴ by reaction of phthalic anhydride with hydrogen peroxide,⁵ and by stirring phthalic anhydride with mildly alkaline peroxide.⁶ The method described here is a slight modification of the last procedure.

4. Merits of Preparation

The Böhme procedure^{2,4} for preparing perphthalic acid from phthalic anhydride and hydrogen peroxide is sensitive to slight variations in the experimental conditions.^{5,6} The present method gives reproducible yields with quite short reaction times.

¹ Shell Development Company, Emeryville, Calif.

² H. Böhme, *Org. Syntheses Coll. Vol.* **3**, 619 (1955).

³ A. Baeyer and V. Villiger, *Ber.*, **34**, 764 (1901).

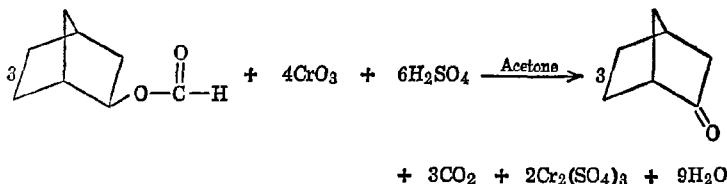
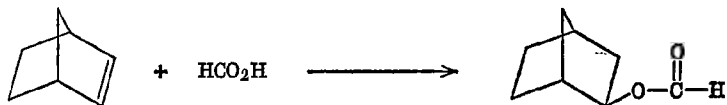
⁴ H. Böhme, *Ber.*, **70**, 379 (1937); G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, **9**, 307 (1944).

⁵ E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955).

⁶ G. B. Payne, *J. Org. Chem.*, **24**, 1354 (1959).

2-NORBORNANONE

(Norcamphor)

Submitted by DONALD C. KLEINFELTER and PAUL VON R. SCHLEYER.¹Checked by WILLIAM E. PARHAM, WAYLAND E. NOLAND, and
LYNETTE E. CHRISTENSEN.

1. Procedure

A. *2-exo-Norbornyl formate*. Approximately 800 g. (17.4 moles) of 98–100% formic acid (Note 1) is added to 400 g. (4.25 moles) of norbornene (Note 2) in a 2-l. round-bottomed flask equipped with a condenser, and the mixture is boiled under reflux for 4 hours (Note 3). The dark solution is cooled and the flask arranged for distillation using a 30-cm. Vigreux column. The excess formic acid is removed under reduced pressure (b.p. 26–30°/21–30 mm.). Distillation of the residue then gives a forerun of about 100 ml. of a mixture of formic acid and ester followed by about 485 g. of 2-*exo*-norbornyl formate, a colorless oil, b.p. 65–67°/14–16 mm., n_D^{25} 1.4594–1.4597. Another 55–65 g. of ester is obtained by adding water to the forerun, extracting with 30–60° petroleum ether, washing the extracts with dilute sodium carbonate solution, dry-

ing over sodium sulfate, and distilling. The total yield is 540–550 g. (90.5–92.5%) (Note 4).

B. *2-Norbornanone*. A solution of 510 g. (3.64 moles) of 2-*exo*-norbornyl formate in 1.5 l. of reagent grade acetone is contained in a 5-l. three-necked flask equipped with a thermometer, stirrer, and dropping funnel containing 8*N* chromic acid solution (Note 5). The flask is cooled with an ice bath and the oxidant is added at a rate such that the reaction temperature is maintained at 20–30°. Approximately 1870 ml. of oxidant solution is required, completion of the reaction being shown by the persistence of the brownish orange color. A slight excess of oxidant is added, and the solution is stirred overnight at room temperature. Solid sodium bisulfite is added in portions to reduce the excess oxidant.

The reaction mixture is poured into a large separatory funnel. The dark green chromic sulfate sludge, which has formed during the course of the reaction, is separated either by decantation and washing or by drawing it off from the bottom of the funnel. The acetone solution is washed three times with 200–250 ml. portions of an aqueous saturated potassium carbonate solution and finally is dried over anhydrous potassium carbonate. The acetone is removed by distillation through a 30-cm. Vigreux column at atmospheric pressure; benzene may be added near the end to assist in the removal of water by azeotropic distillation. When it is observed that the distillation of solvent is complete and the considerably hotter vapors of product begin to ascend the column, the condenser is removed from the top and replaced by an adapter and collection flask immersed in ice water. The adapter is heated and maintained above 100° by a free flame until the product begins to distil (Note 6). 2-Norbornanone, 335–350 g. (83–87%), distils at 170–173° and crystallizes immediately in the collection flask. The crystals melt at 90–91° (Note 7) and are sufficiently pure for most preparative purposes (Note 8).

2. Notes

1. Baker and Adamson 98–100% formic acid was used.
2. Prepared as described in *Org. Syntheses*, **37**, 65 (1957).

3. Norbornene is not soluble in cold formic acid; initially there are two layers. As heat is applied to the flask, solution occurs and the reaction becomes quite exothermic. It is recommended that a splash trap be mounted at the top of the condenser and that an ice bath be nearby in case the refluxing becomes too rapid. *Caution! Formic acid causes severe burns!*

4. Quite pure 2-*exo*-norborneol, m.p. 127–128°, can be prepared by saponification of 2-*exo*-norbornyl formate in an aqueous ethanolic solution of potassium hydroxide. The product can be isolated in about 85% yield by distillation and boils at 178–179°.

5. The 8*N* chromic acid solution² is prepared by dissolving 534 g. of chromium trioxide in ice water, adding 444 ml. of conc. sulfuric acid carefully, and diluting to 2 l. with water.

6. The product solidifies readily. Care should be taken to prevent clogging of the adapter. Once begun, there is no difficulty if the distillation proceeds smoothly to completion.

7. The melting points given in the literature vary from 90–91° (Ref. 3) to 95.5° (Ref. 4). Pure 2-norbornanone, m.p. 97.2–98.0°, may be made by regeneration from its semicarbazone derivative, m.p. 196.5–197.6°.

8. Gas chromatographic analysis shows this material to have a purity of about 96%. Besides a small amount of water (up to 0.5%) there are two minor impurities. Neither 2-*exo*-norbornyl formate nor 2-*exo*-norbornanol is present, however. Oxidation of 2-*exo*-norbornanol with chromic acid, under a variety of conditions, gives 2-norbornanone contaminated with some starting material.

3. Methods of Preparation

2-Norbornanone is generally prepared from the Diels-Alder adduct of cyclopentadiene and vinyl acetate by hydrogenation, saponification, and oxidation with chromic acid in acetic acid solution.⁵ The present procedure, which gives higher over-all yields in fewer steps, makes use of the superior solvent, acetone, for mild chromic acid oxidations² and of the observation that formate esters of secondary alcohols can be oxidized directly to ketones.⁶

4. Merits of Preparation

2-Norbornanone is a useful starting material for various bicyclic derivatives of theoretical interest. The present procedure provides a convenient method for its preparation and illustrates a general method for the oxidation of formate esters to ketones.

¹ Department of Chemistry, Princeton University, Princeton, New Jersey.

² K. Bowden, I. M. Heibron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **1946**, 39; P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *J. Chem. Soc.*, **1951**, 2402.

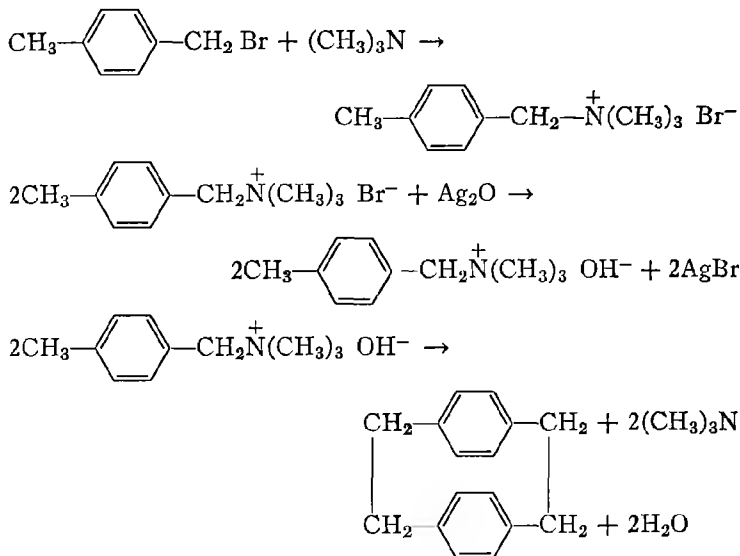
³ G. Komppa and S. Beckmann, *Ann.*, **512**, 172 (1934).

⁴ G. Becker and W. A. Roth, *Ber.*, **67**, 627 (1934).

⁵ K. Alder and H. F. Rickert, *Ann.*, **543**, 1 (1940).

⁶ E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **81**, 6305 (1959).

[2.2]PARACYCLOPHANE

(Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene)Submitted by H. E. WINBERG and F. S. FAWCETT.¹Checked by WILLIAM E. PARHAM, WAYLAND E. NOLAND,
and THOMAS A. CHAMBERLIN.

1. Procedure

*Caution! This preparation should be conducted in a hood to avoid exposure to trimethylamine and to α -bromo-*p*-xylene.*

A. *p*-Methylbenzyltrimethylammonium bromide. In a 1-l. three-necked flask equipped with a stirrer, a reflux condenser provided with a Drierite drying tube, and a gas inlet tube about 1 cm. above the surface of the liquid are placed 600 ml. of dry ether and 100 g. (0.54 mole) of α -bromo-*p*-xylene (Note 1). The flask is cooled in an ice-water bath with stirring. A dry, weighed trap

is cooled in a mush of Dry Ice-acetone, and 50 g. (0.85 mole) of liquid trimethylamine is condensed into the trap. A boiling chip is added to the cold trimethylamine, the trap is connected to the gas inlet tube and is then removed from the cooling bath. The trimethylamine is allowed to distil into the flask during a period of 2 hours, during which time *p*-methylbenzyltrimethylammonium bromide separates as a white solid (Note 2). The resulting pasty mixture is allowed to stand overnight at room temperature. The bromide is collected on a Büchner funnel, the transfer being aided by re-use of the filtrate. The bromide is washed on the filter with 200 ml. of dry ether and dried in air to give 125–130 g. (95–99%) of product (Note 3).

B. [2.2]*Paracyclopentane*. *p*-Methylbenzyltrimethylammonium bromide (24.4 g., 0.10 mole) is dissolved in 75 ml. of water. Silver oxide (23 g.) (Note 4) is added, and the mixture is stirred at room temperature for 1.5 hours. The mixture is filtered, the solid is rinsed with 40 ml. of water, and the combined liquids are collected and then dried azeotropically as follows. A 500-ml. three-necked flask is equipped with a Tlu-bore stirrer with a paddle of "Teflon" tetrafluoroethylene resin, a Dean-Stark water separator² attached to a reflux condenser, and a heating mantle. In the flask are placed 300 ml. of toluene, 0.5 g. of phenothiazine (Note 5), and the above aqueous solution containing the quaternary ammonium hydroxide. The mixture is stirred and heated under reflux during about 3 hours, the water being separated as it collects in the separator. When the water has been removed, decomposition occurs, as indicated by trimethylamine evolution and the separation of solid polymer. Heating and stirring are continued for 1.25 hours, after which time the evolution of trimethylamine has virtually ceased. The mixture is cooled, the solid is separated by filtration, and the somewhat gelatinous solid is extracted overnight in a Soxhlet apparatus (Note 6) employing the toluene used in the azeotropic drying step. After extraction there remains 5.7–6.7 g. of air-dried insoluble poly-*p*-xylylene. The toluene extract is concentrated to dryness under reduced pressure, and the solid residue is washed with three 10-ml. portions of acetone. Sublimation of the remaining solid at 0.5–1.0 mm. (temperature of oil bath 150–160°) gives a sublimate of

1.0–1.1 g. (10–11%; Note 7) of white, crystalline [2.2]paracyclophane, m.p. 284–287° (sealed capillary tube).

2. Notes

1. The α -bromo-*p*-xylene was obtained from Eastman Organic Chemicals; it melted at 35–36.5°.

2. A convenient, alternative procedure consists in slowly passing trimethylamine directly from a cylinder through a trap into the reaction mixture until an excess is present.

3. *p*-Methylbenzyltrimethylammonium bromide is not noticeably hygroscopic. The crude product, after it has been dried at 80° under reduced pressure over phosphorus pentoxide, melts at 197–199°. Recrystallization from absolute ethanol followed by similar drying gives crystals melting at 199–200°. Less thoroughly dried samples show lower and erratic melting points.

4. The silver oxide used may be the commercially available material or that freshly prepared by adding, with stirring, 8.8 g. of sodium hydroxide in 80 ml. of water to a solution of 34 g. of silver nitrate in 200 ml. of water. The precipitate is collected by filtration and washed with water to remove the bulk of the alkali. The wet cake is used directly for preparation of the quaternary hydroxide. The strongly basic quaternary hydroxide solution should be protected from excessive exposure to air because of carbon dioxide absorption.

5. The addition of a polymerization inhibitor appears to increase the amount of paracyclophane formed in the reaction.

6. The polymer is bulky when swollen by the toluene; a Soxhlet thimble 12 cm. long and 145 mm. in diameter is used. Additional toluene may be used in the extraction.

7. The checkers' yields are reported; the submitters report yields of 1.75–2.05 g. (17–19%).

3. Methods of Preparation

The above procedures are essentially those described by Winberg, Fawcett, Mochel, and Theobald.³ Equally good results have been obtained starting with α -chloro-*p*-xylene, but the hy-

grosopic nature of *p*-methylbenzyltrimethylammonium chloride makes this intermediate less convenient to use than the bromide. [2.2]Paracyclophane has been isolated from the pyrolysis of *p*-xylene⁴ and by dimerization of *p*-xylylene.⁵ Paracyclophanes have been synthesized by intramolecular Wurtz reactions at high dilution.⁶

4. Merits of Preparation

This reaction, a 1,6-elimination of the Hofmann type, gives [2.2]paracyclophane from readily available starting materials without requiring complex equipment or manipulations, and, accordingly, it is probably the most convenient method of preparing [2.2]paracyclophane. This substance is of interest because of its unusual geometrical features.⁶ The method is fairly general. Thus in addition to the hydrocarbon [2.2]paracyclophane, heterocyclophanes have been prepared by similar procedures.³ The thiophene derivative, 5,5'-ethylene-1,2-bis-(2-thienyl)-ethane, has been made in 19% yield and the furan derivative, 5,5'-ethylene-1,2-bis-(2-furyl)-ethane, has been made in 72% yield. A monomeric intermediate, 2,5-dimethylene-2,5-dihydrofuran, was isolated in the latter case.

¹ Contribution No. 672 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington 98, Delaware.

² S. Natelson and S. Gottfried, in E. C. Horning, *Organic Syntheses Coll. Vol. 3*, p. 382, John Wiley and Sons, Inc., New York, 1955.

³ H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.*, **82**, 1428 (1960); J. L. Anderson and H. E. Winberg, U. S. pat. 2,876,216 (March 3, 1959); H. E. Winberg, U. S. pat. 2,904,540 (Sept. 15, 1959); F. S. Fawcett, U. S. pat. 2,757,146 (July 31, 1956); T. E. Young, U. S. pat. 2,999,820 (1961).

⁴ C. J. Brown and A. C. Farthing, *Nature*, **164**, 915 (1949); C. J. Brown, *J. Chem. Soc.*, **1953**, 3265.

⁵ L. A. Errede, R. S. Gregorian, and J. M. Hoyt, *J. Am. Chem. Soc.*, **82**, 5218 (1960).

⁶ D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951).

This yields the crude isobiuret as a very pale-yellow granular solid, which is collected by suction filtration, washed with successive small portions of water, drained well, and allowed to dry at room temperature. The dry product is dissolved in 120–150 ml. of boiling benzene. Small quantities of suspended yellow powdery material (and possibly droplets of water) are removed by gravity filtration through a heated funnel or by suction filtration through a preheated Büchner funnel. The clear yellow filtrate deposits large prismatic crystals of 1-phenyl-2-thio-4-methylisobiuret, which are collected by suction filtration at room temperature, washed with a little benzene, and air-dried. The yield of material having a melting point in the range of 122–128° is 27–31.5 g. (65–75%) (Note 3). Further small quantities (2–4 g.) of less pure material may be obtained by partial vacuum evaporation of the combined mother liquors and washings.

B. *1-Phenyl-2-thiobiuret*. A solution of 20.9 g. (0.1 mole) of 1-phenyl-2-thio-4-methylisobiuret in 200 ml. of hot absolute ethanol is treated with 40 ml. of concentrated hydrochloric acid, and the clear liquid is heated under reflux until no more methyl chloride is evolved (6–12 minutes, Note 4). The resulting solution is stirred into 2 l. of water, and the separated crystalline precipitate is collected after storage at 0° for at least 24 hours. The dried product is dissolved in boiling absolute ethanol (5–6 ml. per g.), then the hot solution is quickly filtered by light suction and diluted with half its volume of petroleum ether (b.p. 60–80°). The separated 1-phenyl-2-thiobiuret is collected by suction filtration after storage for 12 hours at room temperature, and rinsed with small portions of a mixture of equal volumes of ethanol and petroleum ether. The yield of product, m.p. 159–161° (Note 5), is 8.8–10.5 g. (45–54%) (Note 6).

2. Notes

1. Methylisourea hydrochloride is accessible from commercially available calcium cyanamide by the method described in *Organic Syntheses*.³

2. The reaction is complete when a withdrawn sample of the liquid, stirred on a watch-glass in an air current, solidifies rapidly and smells only very faintly of phenyl isothiocyanate.

3. This product, though still pale yellow, is suitable for most synthetic purposes. Colorless glass-like prisms of m.p. 128–130° (cor.) are obtainable on further crystallization from benzene.

4. The top of the condenser is fitted with a short vertical piece of hard-glass tubing at the mouth of which the escaping methyl chloride may be burned off. The completeness of the reaction is indicated when insufficient gas is evolved to support a *steady* flame. Methyl chloride will continue to diffuse out and produce a flickering flame when a match is held to the outlet. Prolonging the reaction time excessively reduces the yield.

5. Rather variable melting points have been reported for this compound, probably because the melting is accompanied by decomposition. In a bath heated at about 2° per minute, the checkers obtained capillary tube melting points for all samples in the range 149.5–152° (cor.).

6. The submitters report that partial evaporation of the mother liquors gives additional small quantities of low-melting fractions from which additional pure material may be obtained by further crystallizations. In contrast, the checkers obtained nearly one-half the yield in a second crop which had essentially the same melting point as the first crop. This somewhat different behavior may result from a difference in solvent characteristics of different samples of petroleum ether.

3. Methods of Preparation

1-Phenyl-2-thiobiuret has been prepared by the pyrolysis, at 75–90°, of 1-phenyl-2-thio-4-methylisobiuret hydrochloride,⁴ and by the condensation of carbamyl isothiocyanate with aniline.⁵ The method here described, which is based on the former method, is regarded as most convenient. A comprehensive review of syntheses of biurets, thiobiurets, and dithiobiurets is available.⁶

4. Merits of Preparation

This synthesis is generally applicable. For example, condensation of phenyl isothiocyanate and ethylisourea by the procedure above gives 70–80% yield of 1-phenyl-2-thio-4-ethylisobiuret,⁴ which forms lustrous massive prisms, m.p. 98–99° (from benzene).

¹ Royal Free Hospital School of Medicine, University of London, England.

² P. S. Pinkney, *Org. Syntheses*, Coll. Vol. 2, 116 (1943).

³ F. Kurzer and A. Lawson, *Org. Syntheses*, 34, 67 (1954).

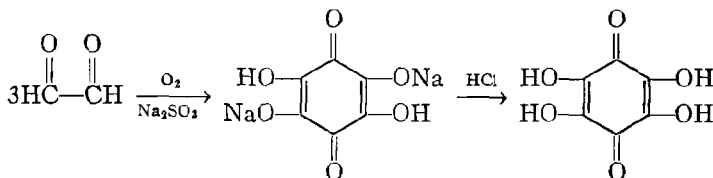
⁴ W. M. Bruce, *J. Am. Chem. Soc.*, 26, 449 (1904); F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 1958, 379.

⁵ L. Birkenbach and K. Kraus, *Ber.*, 71, 1492 (1938).

⁶ F. Kurzer, *Chem. Revs.*, 56, 95 (1956).

TETRAHYDROXYQUINONE

(Quinone, tetrahydroxy-)



Submitted by A. J. FATIADI and W. F. SAGER.¹

Checked by B. C. MCKUSICK and J. K. WILLIAMS.

1. Procedure

A 5-l., three-necked round-bottomed flask is fitted with a thermometer, an air-inlet tube of 10-mm. diameter extending to within approximately 1 cm. of the bottom, and an outlet tube connected to an aspirator (Note 1). A solution of 400 g. (3.17 moles) of anhydrous sodium sulfite and 150 g. (1.79 moles) of anhydrous sodium bicarbonate (Note 2) in 3 l. of water is heated to 40–45° in the flask. Six hundred grams (480 ml., 3.11 moles) of 30% glyoxal solution (Note 3) is added, and a brisk stream of air is drawn through the solution for 1 hour without application of heat. Within a few minutes, greenish black crystals of the sodium salt of tetrahydroxyquinone begin to separate. The flask is warmed to between 80° and 90° over a period of an hour. The air current is then stopped, and the mixture is heated to incipient boiling and set aside for 30 minutes. It is then cooled to 50°

(Note 4), and the sodium salt of tetrahydroxyquinone is separated by filtration and washed successively with 50 ml. of cold 15% sodium chloride solution, 50 ml. of cold 1:1 methanol-water, and 50 ml. of methanol. The air-dried salt weighs 20–21 g.

The salt is added to 250 ml. of 2*N* hydrochloric acid, and the mixture is heated to incipient boiling. The resultant solution is cooled in an ice bath, and the glistening black crystals of tetrahydroxyquinone that precipitate are collected on a Büchner funnel and washed with ice water to give 11–15 g. (6.2–8.4%) of product. The quinone fails to melt on a hot plate at 320° (Note 5).

2. Notes

1. A tube of 10-mm. diameter is necessary to prevent the clogging of the outlet that occurs if tubing of smaller diameter is used.

2. Equivalent amounts of hydrated salt may be used.

3. Dow commercial grade 30% glyoxal solution is satisfactory.

4. It is not necessary to cool below this temperature since crystallization is essentially complete at 50°.

5. This material is pure enough for reduction to hexahydroxybenzene² and most other purposes. A purer product can be obtained by dissolving the crude tetrahydroxyquinone in acetone and adding petroleum ether of b.p. 60–80° to precipitate it.

3. Methods of Preparation

The procedure employed for tetrahydroxyquinone is based on an observation by Homolka.³ Tetrahydroxyquinone may also be prepared by treatment of the glyoxal-bisulfite addition compound with sodium carbonate³ or magnesium hydroxide and potassium cyanide⁴ or by treatment of 50% glyoxal with sodium hydro-sulfite.⁵

4. Merits of the Preparation

Tetrahydroxyquinone is of interest because of its application in analytical chemistry to the determination of barium and as a complexing agent for many ions.⁶ Moreover, it serves as a convenient

source not only of the reduction product hexahydroxybenzene² but also of the oxidation products rhodizonic acid and triquinoyl and of the product of catalytic reduction, *meso*-inositol.

This procedure serves as a particularly simple method for preparing tetrahydroxyquinone. The low yield is more than offset by the simplicity of the set-up, the ease of manipulation, and the low cost and ready availability of the starting materials.

¹ Department of Chemistry, The George Washington University, Washington 6, D. C.

² A. J. Fatiadi and W. F. Sager, this volume, p. 66.

³ B. Homolka, *Ber.*, **54**, 1393 (1921).

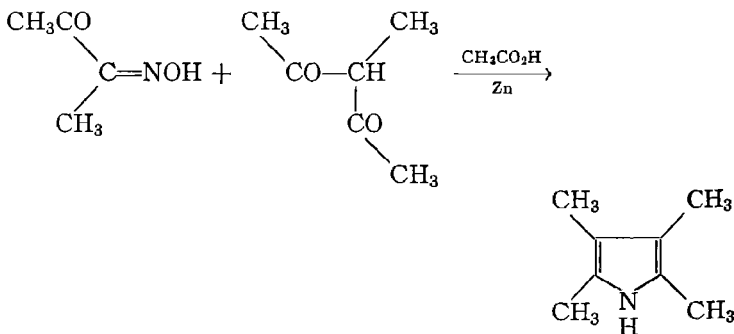
⁴ R. Kuhn, G. Quadbeck, and E. Röhm, *Ann.*, **565**, 1 (1949).

⁵ B. Eistert and G. Bock, *Angew. Chem.*, **70**, 595 (1958).

⁶ J. H. Yoe and L. A. Sarver, *Organic Analytical Reagents*, John Wiley and Sons, Inc., New York, 1941 (out of print); S. J. Kocher, *Ind. Eng. Chem., Anal. Ed.*, **9**, 331 (1937).

2,3,4,5-TETRAMETHYLPYRROLE

(Pyrrole, 2,3,4,5-tetramethyl-)



Submitted by A. W. JOHNSON and R. PRICE.¹

Checked by VIRGIL BOEKELHEIDE and M. KUNSTMANN.

1. Procedure

In a 2-l. three-necked flask fitted with a stirrer, thermometer, and reflux condenser are placed 250 ml. of glacial acetic acid,

54.5 g. (0.84 g. atom) of zinc dust, and 52.5 g. (0.46 mole) of 3-methylpentane-2,4-dione (Note 1). The contents of the flask are stirred vigorously (Note 2), and a solution of 42 g. (0.415 mole) of diacetyl monoxime² in 150 ml. of glacial acetic acid is added from a separatory funnel at a rate to maintain the temperature of the mixture at 65–70°. The addition takes 1 hour. When the addition is complete, the mixture is refluxed with stirring for an additional 30 minutes. The flask is then fitted for distillation with steam under nitrogen; 500 ml. of water is added and steam is introduced. Steam distillation (Note 3) is continued until no more tetramethylpyrrole comes over. This takes 1–2 hours and the distillate amounts to 1–2 l. The tetramethylpyrrole crystallizes from the steam distillate and is collected by filtration, washed with water, and dried over phosphorus pentoxide in a vacuum desiccator. There is obtained 15–18 g. of white plates, m.p. 110–111° (lit.,³ m.p. 112°).

By neutralizing the filtrate with sodium hydroxide solution, a second crop of 4–5 g. of tetramethylpyrrole, m.p. 109–110°, is obtained. The total yield is 20.5–22.5 g. (40–44%) (Note 4).

2. Notes

1. 3-Methylpentane-2,4-dione is prepared by the methylation of acetylacetone.^{4,5}

2. It is essential that the zinc dust be stirred effectively or the reaction may become violent.

3. Tetramethylpyrrole must be prevented from blocking the condenser. From time to time the condenser is cleared by turning off the coolant water.

4. 2,3,4,5-Tetramethylpyrrole is very readily oxidized in the air to a green resinous substance. If it is not used immediately, it should be stored under nitrogen or sealed in a glass vial under vacuum.

3. Methods of Preparation

2,3,4,5-Tetramethylpyrrole has been prepared by the action of sodium methoxide on 2,3,5-trimethylpyrrole,⁶ by the reduction of 2,3,5-trimethylpyrrole-4-aldehyde semicarbazone with sodium

ethoxide,⁷ by the reduction of 2,3,4-trimethylpyrrole-5-aldehyde with sodium ethoxide and hydrazine hydrate,⁸ and by the reduction of 2,4-dimethylpyrrole-3,5-dicarboxylic acid with lithium aluminum hydride.⁹ Direct ring synthesis by the condensation of 3-aminobutan-2-one and butan-2-one in alkaline solution gave very poor yields, the principal product being 2,3,5,6-tetramethylpyrazine.³ The above modification of direct ring synthesis avoids this side reaction.¹⁰

4. Merits of Preparation

The present method possesses these advantages over those reported earlier: ⁵⁻⁸ it is less laborious, in that it is a single-stage preparation, and it gives a better over-all yield.

¹ Department of Chemistry, The University of Nottingham, Nottingham, England.

² W. L. Semon and V. R. Damerell, *Org. Syntheses, Coll. Vol. 2*, 204 (1943).

³ H. Fischer and B. Walach, *Ann.*, **447**, 38 (1926).

⁴ A. W. Johnson, E. Markham, and R. Price, this volume, p. 75.

⁵ K. von Auwers and H. Jacobsen, *Ann.*, **426**, 161 (1921).

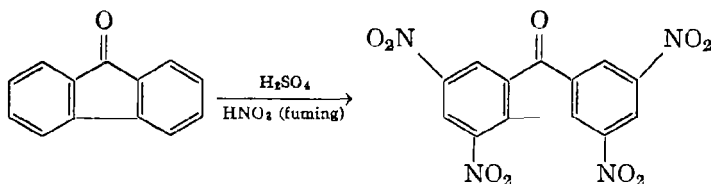
⁶ H. Fischer and E. Bartholomäus, *Z. physiol. Chem.*, **80**, 10 (1912).

⁷ H. Fischer and W. Zerweck, *Ber.*, **56**, 519 (1923).

⁸ M. Dennstedt, *Ber.*, **22**, 1924 (1889).

⁹ A. Treibs and H. Derra-Scherer, *Ann.*, **589**, 188 (1954).

¹⁰ A. W. Johnson, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, **1958**, 4254.

2,4,5,7-TETRANITROFLUORENONE**(9-Fluorenone, 2,4,5,7-tetranitro-)**Submitted by MELVIN S. NEWMAN and H. BODEN.¹

Checked by WILLIAM E. PARHAM, PETER DELVIGS, and E. LEETE.

1. Procedure

A 5-l. three-necked flask fitted with an all-glass addition funnel and two condensers is charged with 770 ml. of concentrated sulfuric acid and 1.3 l. of 90% fuming nitric acid (Note 1). The solution is heated under gentle reflux, and a solution of 73 g. (0.4 mole) of 9-fluorenone (Note 2) in 840 ml. of concentrated sulfuric acid (Note 3) is added from the dropping funnel over a 1-hour period. After the fluorenone addition is complete, a solution of 950 ml. of fuming nitric acid in 1120 ml. of concentrated sulfuric acid is added dropwise during 8.5 hours to the gently refluxing reaction mixture. The heating jacket is turned off and the solution is allowed to stand for 10 hours. The reaction mixture is poured into 5 gallons of water in two 5-gal. crocks (Note 4). The light yellow precipitate is washed with water, twice by decantation, filtered, washed several times with water and sucked dry, and finally is dried in a vacuum oven at 80° for 10 hours (Note 5). The yield of crude 2,4,5,7-tetranitrofluorenone, m.p. 249–253°, is 105–117 g. (72–80%). This solid is recrystallized from 1.6 l. of acetic acid containing 100 ml. of acetic anhydride. The hot solution is filtered through a fluted filter and cooled rapidly to yield 80–86 g. (51–54%) of 2,4,5,7-tetranitrofluorenone, m.p. 253.0–254.5° cor. (Notes 6 and 7).

2. Notes

1. Baker Analyzed reagent grade fuming nitric acid may be added to the sulfuric acid without special precautions, since the heat effect is not large.

2. Eastman white label 9-fluorenone, m.p. 82–84°, was used. The checkers used material, m.p. 83.5–84.5°, prepared from fluorene.²

3. The deep purple-brown solution may have to be warmed in order to dissolve all the fluorenone.

4. This operation must be carried out in the hood.

5. The product may be dried under reduced pressure over calcium chloride for several days.

6. Additional product amounting to 15–17% may be obtained by recrystallization of further crops from the mother liquor.

7. Tetranitrofluorenone crystallizes with 0.5 mole of acetic acid which is readily lost on heating under reduced pressure.

3. Methods of Preparation

The procedure described here is essentially that of Newman and Lutz.³ 2,4,5,7-Tetranitrofluorenone has been prepared by nitration of fluorenone,⁴ 2,4,7-trinitrofluorenone,^{5,6} and 4,5-dinitrofluorenone.⁶ The preparation by Schmidt et al.,^{4,6} which supposedly yielded the 2,3,6,7-isomer, has been shown⁶ to yield the 2,4,5,7-isomer.

4. Merits of Preparation

The complexes which 2,4,5,7-tetranitrofluorenone forms with aromatic compounds are in general higher melting and less soluble than are the corresponding complexes of 2,4,7-trinitrofluorenone.^{3,7}

¹ Department of Chemistry, Ohio State University, Columbus, Ohio.

² E. B. Hershberg and I. S. Cliff, *J. Am. Chem. Soc.*, **53**, 2720 (1931).

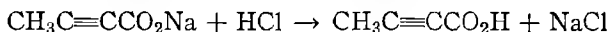
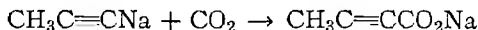
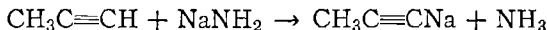
³ M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956).

⁴ J. Schmidt, F. Retzlaff and A. Haid, *Ann.*, **390**, 210 (1912).

⁵ J. Schmidt and K. Bauer, *Ber.*, **38**, 3758 (1905).

⁶ F. E. Ray and W. C. Francis, *J. Org. Chem.*, **8**, 52 (1943).

⁷ M. Orchin, L. Reggel, and E. O. Woolfolk, *J. Am. Chem. Soc.*, **69**, 1225 (1947).

TETROLIC ACID**(2-Butynoic Acid)**

Submitted by J. C. KAUER and M. BROWN.¹

Checked by W. E. PARHAM, WAYLAND E. NOLAND, and
RICHARD J. SUNDBERG.

1. Procedure

A 3-l., three-necked, round-bottomed flask is equipped with a glass paddle stirrer, a condenser containing a mixture of acetone and solid carbon dioxide, and a gas inlet tube. The outlet of the condenser is protected from the atmosphere by a T-tube through which a slow stream of nitrogen is passed. The flask is purged with nitrogen, and about 1.5 l. of anhydrous liquid ammonia is either poured or distilled into the flask. A small crushed crystal of ferric nitrate nonahydrate is added, followed by 23 g. (1 g. atom) of freshly cut sodium in small pieces (Note 1).

Methylacetylene (44–48 g., 1.1–1.2 mole) (Note 2) is bubbled in through the gas inlet tube with rapid stirring. Sodium methylacetylide precipitates as a flocculent gray solid. The solid carbon dioxide is removed from the condenser, and the ammonia is evaporated overnight under a slow stream of nitrogen. A hot water bath may be used to drive off residual ammonia. One liter of dry tetrahydrofuran (Note 3) and 500 ml. of anhydrous ether are added, and with rapid stirring a slow stream of anhydrous carbon dioxide from a cylinder is passed into the mixture (Note 4). After 8 hours the rate of absorption of carbon dioxide is very slow. Any solid caked on the inside walls of the flask should be scraped off with the glass paddle stirrer. A very slow flow of carbon dioxide is continued overnight (Note 5).

The solvent is removed as completely as possible by distillation on a steam bath under water-pump vacuum. Two hundred milliliters of water is added, and the solid is dissolved by swirling the flask (Note 6). The solution is filtered if suspended solid is present. The aqueous solution is extracted twice with 100-ml. portions of ether. The aqueous layer in a 1-l. Erlenmeyer flask is then cooled in ice, and a mixture of 70 ml. of concentrated hydrochloric acid and 200 g. of ice is added slowly with swirling. The acidified solution is continuously extracted with 200 ml. (or more) of ether for 24–36 hours. The extract is evaporated in a stream of air or nitrogen to give tetrolic acid in the form of a mushy tan solid that is further dried in a vacuum desiccator over concentrated sulfuric acid for 2 days (Note 7). The product is a tan crystalline solid weighing 58–60 g. (69–71% based on sodium) and melting at 71–75°. It is purified further by addition to 700 ml. of boiling hexane. As soon as the tetrolic acid has dissolved, about 1 g. of activated carbon is added, and the solution is filtered through a heated funnel (Note 8). The filtrate is refrigerated (5°) overnight and 42–50 g. (50–59%) (Note 9) of tetrolic acid is collected in the form of white needles, m.p. 76–77°. A second recrystallization from hexane gives tetrolic acid melting at 76.5–77° (Note 10).

2. Notes

1. The first few pieces of sodium should be converted to sodium amide as evidenced by a color change from blue to gray. The rest of the sodium is then added over a period of 30 minutes.

2. An excess may be used if the purity of the methylacetylene is in doubt; however, a large excess will result in foaming when the liquid ammonia is later evaporated. Methylacetylene of satisfactory purity is available from the Matheson Company.

3. The tetrahydrofuran is distilled from sodium and stored under nitrogen.

4. When a flow rate of 70–100 ml. per minute is used, the internal temperature does not rise above 30° and most of the carbon dioxide is absorbed. A lower yield (50%) of product is obtained when carbon dioxide gas is generated by the slow evaporation of commercial solid carbon dioxide.

5. The reaction is complete when the addition of a small amount of the solid to a few drops of water yields a solution with a pH below 10.

6. Residual tetrahydrofuran may separate as a second (upper) phase. It is removed by the ether extraction.

7. To avoid spattering of the solid the desiccator is evacuated slowly. If drying is incomplete, an aqueous layer will be left in the hexane solution when the tetrolic acid is recrystallized.

8. Prolonged boiling should be avoided since some tetrolic acid is lost by volatilization.

9. The submitters obtained yields of tetrolic acid as high as 67.2 g. (80%).

10. In one run the submitters passed excess methylacetylene (1.6 moles) into a solution of sodium in liquid ammonia until the color turned from blue to white. No ferric nitrate was used. This somewhat shorter procedure yielded pure white sodium methylacetylide and did not diminish the yield of tetrolic acid. Excess methylacetylene is necessary because 0.5 mole is converted to propylene.

3. Methods of Preparation

Tetrolic acid has been prepared by treatment of acetoacetic ester with phosphorus pentachloride followed by dehydrochlorination of the reaction products;² by the base-catalyzed isomerization of 3-butyric acid;³ and by the treatment of 4,4-dibromo-3-methyl-2-pyrazolin-5-one with alkali followed by acidification.⁴

It has also been prepared by the carbonation of sodium methylacetylide under pressure,^{5,6} in ether suspension,⁷ and in the dry state.⁸

4. Merits of Preparation

The virtue of the present method is its convenience, especially when pressure equipment is not available. This method is probably generally applicable to the synthesis of acetylenecarboxylic acids from terminal acetylenes. Thus phenylpropionic acid was prepared from phenylacetylene in 51% yield by the present procedure.

¹ Contribution No. 555 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company.

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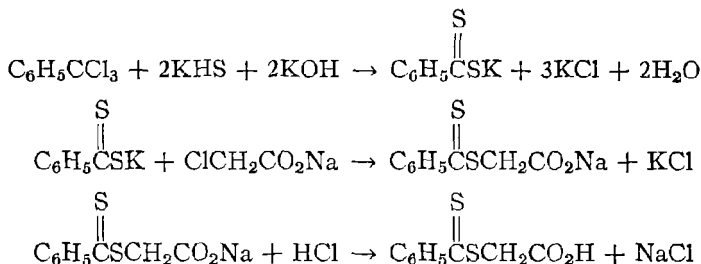
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THIOBENZOYLTHIOGLYCOLIC ACID

(Benzoic acid, dithio-, carboxymethyl ester)



Submitted by FREDERICK KURZER and ALEXANDER LAWSON.¹

Checked by MAX TISHLER, G. A. STEIN, W. F. JANKOWSKI.

1. Procedure

A solution of alcoholic caustic potash, prepared by dissolving 59.3 g. of 85% potassium hydroxide (0.90 mole) in 400 ml. of absolute ethanol with warming, is divided into two equal portions, one of which is saturated with hydrogen sulfide at room temperature (Note 1). The recombined solutions are placed in a 1-l. three-necked flask fitted with a Hershberg stirrer (Note 2), a gas delivery tube (Note 3), and a reflux condenser carrying a dropping funnel (Note 4). The air is displaced from the apparatus by passing a stream of nitrogen through the stirred liquid (Note

5). The solution is warmed to approximately 45–50°, and 49 g. (35 ml., 0.25 mole) of benzotrichloride is added dropwise through the condenser from a dropping funnel at a rate to maintain the temperature of the reaction mixture at approximately 60°; this requires 1–1.5 hours (Note 6). The reaction mixture turns deep red soon after the addition is started. When all the benzotrichloride has been added, the stirred deep-red suspension is refluxed gently for 30 minutes. A solution of 33.1 g. (0.35 mole) of chloroacetic acid in 200 ml. of water, neutralized with 29.4 g. (0.35 mole) of solid sodium bicarbonate, is next rapidly added through the condenser, the stirred mixture heated to boiling as rapidly as possible and refluxed (Note 5) for 5 minutes.

The resulting brownish red suspension is added to 750–1000 g. of ice contained in a 2-l. beaker (Note 7) and the turbid orange solution slowly acidified (to Congo red) with good stirring (Note 8) by the addition of approximately 50 ml. (Note 9) of concentrated hydrochloric acid. The deep-scarlet crystalline precipitate is collected at the pump after 30 minutes at 0° and rinsed with small quantities of water.

The air-dried product is crystallized by dissolving it in chloroform (approximately 120 ml.), followed by dilution of the filtered boiling liquid (Note 10) with hot petroleum ether (boiling range 60–80°, 60–80 ml.). The crystalline product, which separates rapidly, is collected at 0°, rinsed on the filter with a mixture of chloroform and petroleum ether (1:3), and dried. The yield of magnificent deep-scarlet lustrous prisms, m.p. 127–128°, varies between 28.9 and 30.4 g. (54–57% of the theoretical). Concentration of the combined filtrates and wash liquids under reduced pressure to a small volume (50–80 ml.) yields an additional small quantity (1.5–3.0 g., 3–6%) of material of satisfactory purity, m.p. 121–124°.

2. Notes

1. Saturation is complete when a slow stream of gas is passed through the solution during 2.5–3 hours. The initially turbid liquid generally clears and remains nearly colorless during this process.

The checkers on several occasions obtained a small amount of a flocculent precipitate that most probably was potassium carbonate.

2. The checkers used a Trubore stirrer with a Teflon paddle.

3. The delivery tube is fitted to allow the stream of nitrogen to enter as far under the surface of the liquid as possible without obstructing the operation of the stirring device.

4. The checkers used a pressure-equalizing dropping funnel.

5. The passage of nitrogen is continued throughout the experiment.

6. The exothermic nature of the reaction maintains the temperature of the mixture between 50° and 60°, depending upon the rate of the addition of the benzotrichloride.

7. The checkers used a 3-l., wide-necked, round-bottomed flask equipped with a mechanical stirrer.

8. Some unmelted ice should remain during the acidification, which is carried out slowly at 0°, to prevent the separation of the crude material in the form of an oil.

9. The checkers found that 25–30 ml. of concentrated hydrochloric acid was sufficient.

10. The submitters filtered the solution rapidly with suction through a preheated Büchner funnel. The checkers found that the product often crystallized too rapidly and plugged the filter. As a result, the crude product was dissolved in an excess of chloroform (160–175 ml.), then filtered, and the excess solvent evaporated before dilution with light petroleum ether. In some cases, no filtration was necessary because the chloroform solution was clear.

3. Methods of Preparation

Thiobenzoylthioglycolic acid has been prepared by the interaction of potassium dithiobenzoate and alkali chloroacetate.²⁻⁴ The required intermediate, dithiobenzoic acid, has been obtained from phenylmagnesium bromide and carbon disulfide,^{2,3,5} or by the condensation of benzaldehyde and hydrogen polysulfides,^{2,6} or most conveniently by treatment of benzotrichloride with potassium hydrogen sulfide.^{2,4,7} The last procedure has been adapted here to afford improved yields.

4. Merits of Preparation

Thiobenzoylthioglycolic acid is a useful thiobenzoylating agent,^{2-4,8-12} and the resulting products find application for the synthesis of various heterocycles. These applications of thiobenzoylthioglycolic acid have recently been reviewed.¹⁴

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SUBJECT INDEX

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NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

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Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds which are of general interest, as well as procedures which illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products but also for any hazards that may be involved. Full details of all manipulations should be described, and the **range** of yields should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point **range** should be reported, and for each liquid product the **range** of boiling point and refractive index should be included. In some instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, or nuclear magnetic resonance spectra. The methods of preparation or sources of the reactants should be described in notes, and the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where rather standard commercial grades are specified.

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Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

EDITOR'S PREFACE

In the editor's preface to Volume 41, the founding of *Organic Syntheses* was reviewed and it was pointed out that the original purpose of this series was to provide standard procedures for the preparation of organic compounds at a time when very few chemicals were available commercially. This need is no longer as urgent because of the development of commercial sources for a wide variety of starting materials. However, current research has developed other needs no less pressing and, in some respects, more challenging than those of previous years. Of particular concern are the needs for exemplary experiments demonstrating new and general types of reactions and for well-studied procedures illustrating new methods or the preparation of new reagents.

Although *Organic Syntheses* has retained the same format and checking system through the intervening decades, it has moved to meet these needs while continuing to fulfill its original purpose of supplying standard procedures for the preparation of versatile and valuable starting materials. For example, in Volume 42 the preparation of 2,2-difluorosuccinic acid (p. 44) provides a model for the new cycloaddition reactions forming cyclobutanes and illustrates the usefulness of these derivatives for synthetic purposes. The preparation of [2.2]-paracyclophane (p. 83) represents a new and highly useful method of dimerization. The virtues of the rhodium-on-alumina catalyst for effecting *cis* perhydrogenation of aromatic rings without hydrogenolysis are demonstrated in the preparation of hexahydrogallic acid (p. 62). A new application of amine oxide chemistry for effecting nucleophilic substitution is described in the preparation of 2-cyano-6-methylpyridine (p. 30).

With regard to new reagents, the preparation of 3 β -acetoxy-tienic acid (p. 4) provides an outstanding reagent for the resolution of alcohols. 2,4,5,7-Tetranitrofluorenone (p. 95) is valuable both for the characterization of hydrocarbons and as an

intermediate for other reagents used in the resolution of optically active aromatic hydrocarbons. 9,10-Dihydroanthracene (p. 48) is of special value for homolytic hydrogen transfer reactions.

Numerous examples of the preparation of versatile and valuable starting materials are also evident. Current theoretical interest in adamantane is reflected by a convenient procedure for its preparation (p. 8). 2-Cyclopentenone (p. 38) and 2-cyclopenten-1,4-dione (p. 36) are not only useful dienophiles for Diels Alder reactions but also attractive starting materials for a variety of compounds of theoretical interest. Similarly, the preparations of allene (p. 12), tetrolic acid (p. 97), ethylene sulfide (p. 59), and 2-norbornanone (p. 79) provide convenient access to exceptionally useful compounds.

VIRGIL BOEKELHEIDE

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